ELC REVISION

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PRINCIPLES OF ENDOCRINOLOGY

The endocrine system is grouped based on a common signalling mechanism rather than on interrelated functions. It is composed of a number of glands throughout the body that use endocrine signalling to control homeostasis. The endocrine system is a whole-body control system similar to the nervous system, but its effects are usually slower and longer lasting. In addition, the endocrine system communicates with the body via the blood rather than nerves.

- Endocrine signalling involves the release of hormones into the blood to affect different parts of the body
- Paracrine signalling involves the release of hormones into the ECF to affect nearby cells
- Autocrine signalling involves the release of hormones into the ECF to affect the releasing cell itself
- Intracrine signalling involves the production of a hormone within the cell that has intracellular effects
- Juxtracrine signalling involves the production of a hormone that is then used to affect nearby cells using receptors or the ECF

Hormones can be broken into different classes based on their structure:

- Peptide and protein hormones:
    - Composed of chains of amino acids of variable lengths
    - Water and blood soluble – usually unbound
    - Signal through cell-surface receptors as not lipid soluble and cannot cross cell membrane
    - Usually signal through GPCR causing 2nd messenger cascade response and kinase activation
    - Commonly synthesized as prohormones
        - This allows for the production of a 'reservoir' of hormone that can be activated when needed
        - Pro-hormones often have a longer half life
    - Cannot be administered orally in therapeutic treatment because of digestive breakdown
- Amino acid derivatives:
    - Synthesized from amino acids (classically tyrosine, tryptophan and glutamic acid)
    - Some molecules in this class are also produced by neurons and used as neurotransmitters (i.e. catecholamines)
    - Largely signal through cell-surface receptor
        - Exceptions to this include thyroid hormone which is lipid soluble and has intracellular signalling capabilities
    - Cell surface receptor causes TK phosphorylation
- Lipid derivatives:
    - Synthesized from a cholesterol precursor
    - All lipid hormones have a preserved cholesterol backbone structure
    - Largely synthesizes in the adrenal and reproductive glands
    - Are lipid soluble and thus can use cytosolic as well as cell-surface receptors
        - Intracellular responses are usually slower
            - This is because they often rely on genetic transcriptional changes
        - Extracellular responses are usually faster
- Fatty acid derivatives
    - Synthesized from polyunsaturated fatty acids
    - Largely include eicosanoids and arachidonic acids

One hormone can have multiple effects in different tissues. This is because the response of a cell is dependent on the receptor and its actions. Receptors can be broken into the following categories:

- Cell surface receptors: Receptor is located on the cell wall. These can have both positive and negative actions.
    - Tyrosine kinase receptors
        - Work via enzymatic additions of phosphate groups to a second substrate (this can modify the enzyme directly or indirectly via another molecule)
        - These have the ability to be internalized by the cell to modify a response to a substrate
    - G-protein coupled receptors
        - Uses a second messenger system to create a cascade that can amplify the response
- Intracellular receptors: These bind to lipid-soluble substances within the cell (either in the cytosol or the nucleus) and work via the modification of DNA transcription.
    - Some lipid-soluble hormones (particularly steroid hormones) can have both intracellular genomic and non-genomic responses.

Hormones can be transported bound to carrier proteins or free in the blood. Polar hormones are usually stored in vesicles and secreted by exocytosis freely in the blood. Non-polar hormones can be free or bound.

- Bound hormones provide a reservoir or pool of the hormone to minimise fluctuations in hormone levels as well as extending the half-life of the hormone.
- The free hormone hypothesis states that only the free (unbound) hormone is biologically active

The sensitivity of the target cell can be modified to change the response to a hormone:

- Receptor expression can be changed
- Permissiveness: one hormone can increase the effectiveness of another
- Synergism: the combined effect of two hormones together creates a greater response
- Antagonism: one hormone deceases the effectiveness of another

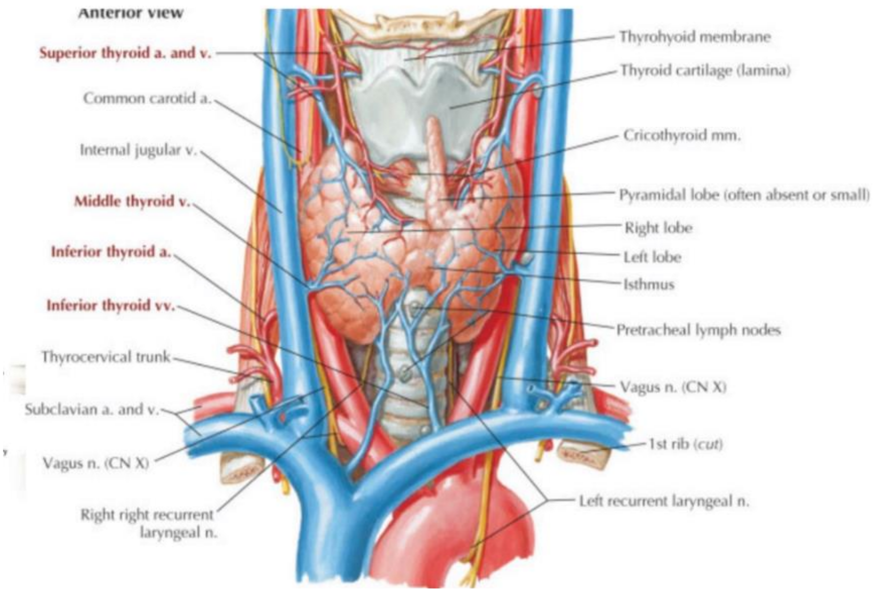
THYROID & PARATHYROID ANATOMY

The thyroid gland is a dual lobed, highly vascular, red H-shaped organ located anteriorly to the larynx, wrapped around the first rings of the cricoid cartilage at the level of C5-T1. It is the largest endocrine gland in the body. It is usually bi-lobed, but a third pyramidal lobe is present in up to 50% of people. It is anchored to the larynx via the isthmus, located in the pretracheal fascia underneath strap muscles. This allows the thyroid gland to move with swallowing.

The top of the thyroid is usually located at the level of the laryngeal prominence and at the same level as the carotid bifurcation. It is surrounded by the pretracheal fascia as well as a true capsule which is relatively thin and extends inwards into the gland to divide and create lobules.

The thyroid relations are as follows:

- Anterolaterally: strap muscles
    - Sternohyoid and thyrohyoid muscles
- Posterolaterally: parathyroid glands, cricoid cartilage, carotid sheath
- Medially: trachea, oesophagus, recurrent laryngeal nerve, superior laryngeal nerve
    - This means that enlargement of the thyroid gland can cause compression of the trachea and/or oesophagus and associated symptoms



The arterial supply of the thyroid includes:

- Superior thyroid artery (branch of external carotid)
    - Supplies upper lateral lobes
- Inferior thyroid artery (branch of the thyrocervical trunk of subclavian artery)
    - Supplies inferior lateral lobes
- Thyroid ima artery
    - Present in a small percentage of people branching from the arch of the aorta or brachiocephalic artery
    - Supplies the isthmus

The thyroid is highly vascular and there are many anastomoses within the thyroid gland.

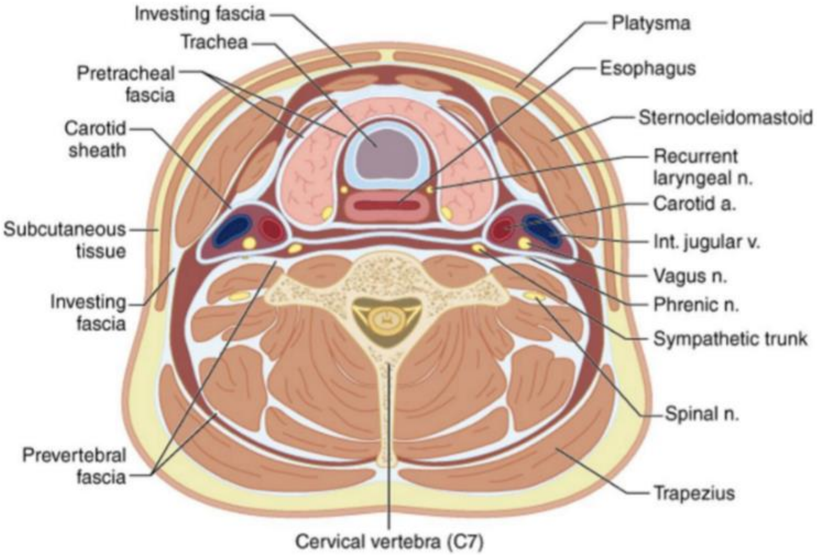
The venous drainage of the thyroid includes:

- Superior thyroid veins internal jugular vein
- Middle thyroid veins internal jugular vein
- Inferior thyroid vein brachiocephalic vein

The thyroid and parathyroid receive:

- Sympathetic innervation from cervical ganglia
- Parasympathetic innervation from the vagus nerve

The thyroid gland is closely related to both the current laryngeal and external laryngeal nerves. These control the intrinsic muscles of the vocal cords and any damage to these can cause pitch changes or hoarseness etc. The thyroid is also closely related to the oesophagus and the trachea and thus enlargement of the gland can cause compressive symptoms in these organs.



The parathyroid glands are small brown-yellow glands located on the posterior aspect of the thyroid. They are contained within a thin fibrous capsule and are usually contained within the pretracheal fascia. They have a highly variable position due to their embryological development. They are not located within the trachea capsule but are located within the pre-tracheal fascia.

- Chief cells are composed of a granular cytoplasm and have a polygonal shape
    - Produce PTH
- Oxyphil cells are slightly larger, non-granular and have an eosinophilic appearance
    - Have no known function

Both the thyroid and parathyroid glands receive the same innervation:

- Sympathetic innervation derived from the cervical ganglia of sympathetic trunk
- Parasympathetic innervation derived from the vagus nerve

The lymph drainage of the thyroid and parathyroid glands is to the deep cervical nodes and paratracheal nodes.

THYROID AND PARATHYROID EMBRYOLOGY

The thyroid gland begins to develop around 24 days post-fertilization (dpf). It is the first endocrine gland to develop in the foetus. The follicular cells of the thyroid are derived from the endoderm while the parafollicular (C cells) are derived from the neural crest via the 4th pharyngeal pouch. The thyroid gland is derived from a midline diverticulum of endoderm in the floor of the pharynx known as the thyroglossal duct (located between the 1st and 2nd pharyngeal arches)

- The thyroid gland migrates downwards through the foramen cecum – the opening of the thyroglossal duct (near the tongue)
- The thyroid gland descends from this point, creating the thyroglossal duct
- The gland travels anterior to the trachea into the hypopharyngeal eminence
- It forms two lateral lobes
    - The thyroid may also form a pyramidal lobe (in the centre, along the thyroglossal duct path) in around 50% of people
- By 4 weeks the gland has reaches its approximate final position
- By 7 weeks of development the thyroid gland has its definitive shape
- The C cells of the thyroid are derived from the IV pharyngeal pouch
- The thyroglossal duct usually degenerates
    - Failure of the duct to degenerate can result in the formation of thyroglossal duct cysts
        - This occurs when the thyroglossal duct remnants fill with fluid

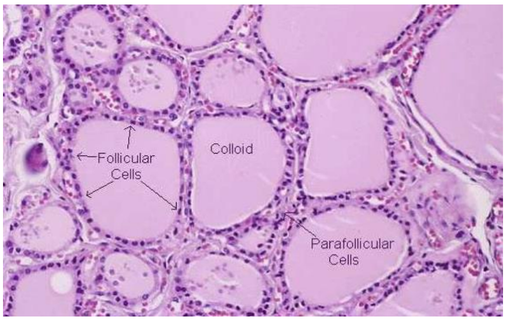
    - Ectopic thyroid glands or sublingual can be found along the path of the thyroglossal duct as high as the base of the tongue in around 10% of autopsies
        - Lingual thyroid refers to the development of the thyroid gland at the base of the tongue

The parathyroid gland is derived from different embryological tissue (endodermal) to the thyroid gland.

- The superior parathyroid glands are derived from the IV pharyngeal pouch
    - The IV pharyngeal pouch is also known as the ultimobranchial body and gives rise to the C cells of the thyroid
- Inferior parathyroid glands are derived from the III pharyngeal pouch

The inferior parathyroid glands have a very variable position due to their embryological development; they are derived from the same tissue as the thymus and usually migrate downwards with this organ, and thus may continue to move further downwards towards this area during development.

THYROID HISTOLOGY



The functional unit of the thyroid is the thyroid follicle. This is a spherical structure surrounded by a single layer of follicular cells that range from squamous to columnar in shape depending on their activity level. The follicle is filled with a pink staining fluid known as colloid.

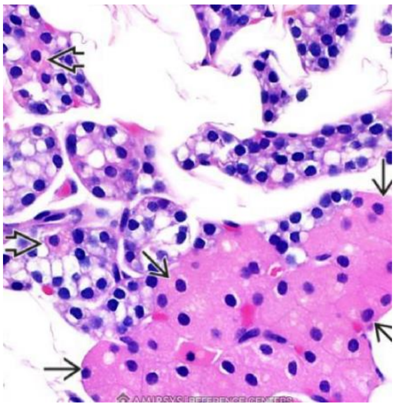
The parafollicular C cells are difficult to see in normal thyroid histological sections but exist between follicles in the stroma of the thyroid. Sometimes immunohistochemical staining can be used to see the parafollicular C cells. These cells are involved in calcium metabolism.

The space between follicles is known as stroma and is composed of loose connective tissue that is continuous with the capsule of the thyroid.

PARATHYROID HISTOLOGY

The normal parathyroid glands have a small capsule containing loosely distinguishable lobules. The stroma of the parathyroid gland is composed of adipocytes (around 50% fat is normal) and fibrous/connective tissue. The ratio of stroma to adipose tissue can be used to assess the functional state of the parathyroid gland; hyperfunctioning parathyroid glands have less stroma.

Chief cells are the primary cell of the parathyroid and secrete PTH. They are polygonal cells with round central nuclei and a pale staining cytoplasm. They are usually arranged in small nests. Oxyphil cells are larger and eosinophilic, but their function is currently unknown.



PANCREAS ANATOMY

The pancreas is a soft, unencapsulated organ that sits retroperitoneally in the abdominal cavity. It sits around the level of the transpyloric plate (L1/2). It is closely related to:

- The duodenum (wraps around the head of the pancreas)
- Superior mesenteric artery and vein
- Spleen (the tail of the pancreas sits near the hilum of the spleen)
- Stomach (in front and above the pancreas)
- IVC and aorta (pancreas sits in front of these)

The exocrine pancreas releases enzymes which contribute to digestion. These are released through the pancreatic duct, which joins with the ducts carrying bile from the liver and gallbladder to form the common bile duct. This then empties into the duodenum.

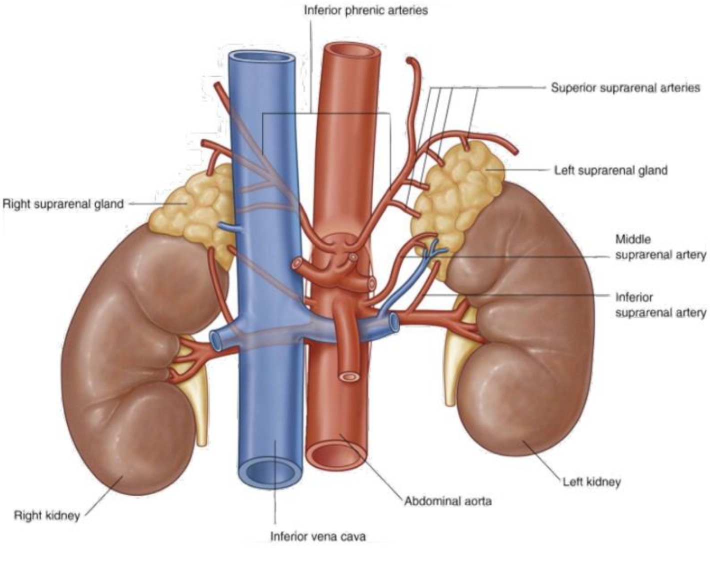
- Blockage of this duct can cause build-up of enzymes which can be serious

The endocrine pancreas releases hormones into the bloodstream.

ADRENAL ANATOMY

The adrenal glands are paired retroperitoneal organs located superior to the kidneys. They are composed of an inner medulla and an outer cortex of different embryological origins. They are both located at the same vertebral level of T12, despite the kidneys being located at different vertebral levels – this is because of the different shapes. They are enclosed in a layer of adipose tissue and the perinephric fascial compartment, separated from the kidneys by a fascial septum. They are firmly adhered to the diaphragm.

- The left adrenal gland is crescentic in shape and sits posterior to the stomach and pancreas
- The right adrenal gland is more pyramidal in shape and sits posterior to the bare area of the liver and is closely associated with the IVC



The cortex is derived by mesodermal tissue and has a yellow-coloured, glandular structure that is external to the medulla. The yellow colour is derived from its high lipoprotein content. The medulla is derived from neuroectoderm and has a brown appearance, sitting inside the cortex. The cortex is broken into three distinct layers of cell types, each with its own function.

- The zona glomerulosa is the outermost layer and is thin. It is composed of ‘glomeruli’ or balls of cells and is responsible for the production of mineralocorticoids (particularly aldosterone)
- The zona fasciculata is the middle layer and is composed of fascicles or cords of cells known as spongiocytes that produce primarily glucocorticoids (i.e. cortisol)
    - This layer is usually lighter staining than the others.

- The zona reticularis is the inner most layer and is composed of a reticular network of cells that appears less organised. These cells produce primarily sex steroids such as DHEA.
- The medulla of the adrenal gland is composed of neural crest derived tissue and has a distinct appearance. It contains chromaffin cells that produce catecholamines.
    - The medulla is under control of the SNS via direct neural connection

The relations of the adrenal glands include:

- Anterior:
    - Left: stomach bed and pancreas body
    - Right: bare area of the liver
- Posterior: abdominal wall

The adrenal glands are highly vascular and receive blood supply from:

- Superior adrenal arteries (6-8 branches from the inferior phrenic artery)
- Middle adrenal artery (1 branch from the abdominal aorta)
- Inferior adrenal artery (1 or 2 branches from the renal arteries)

These arteries branch at the capsule of the adrenal gland and form smaller vessels which pierce the capsule. Once they enter the cortex, they divide into either long or short vessels. Long vessels form a capillary network in the glomerulosa and then another in the medulla, while short vessels form capillary networks in the glomerulosa and the reticularis as well as the medulla. This is evidence that the medulla plays a role in the control and manufacture of the cortical hormones as well as the catecholamines.

The venous drainage of the adrenal gland is a singular adrenal vein which exits at the hilum.

- The left adrenal vein drains into the left renal vein before crossing the aorta and entering the IVC
- The right adrenal vein drains directly into the IVC due to it's close association

The innervation of the adrenal gland is derived from the coeliac plexus and greater splanchnic nerves. Sympathetic innervation to the adrenal medulla occurs via myelinated pre-synaptic fibres, largely originating from the T10-L1 spinal cord segments.

- Post-ganglionic sympathetic fibres also innervate the blood vessels of the adrenal gland in the usual pattern

The lymph drainage from the adrenal gland drains to the lumbar lymph nodes.

ADRENAL GLAND EMBRYOLOGY

The adrenal cortex is derived from the intermediate mesoderm of the foetus. The cells migrate to the approximate site around week 5 post-fertilization. The medullary cells are derived from neural crest cells and migrate to the site at the same time but separately. Initially the cells develop separately to one another, before the cortex envelops the chromaffin cell precursors to form the characteristic medulla.

The cortex develops in two waves; the initial cortex is known as the foetal cortex and is extremely important in foetal development. It is large and produces DHEA which is converted by the placenta to oestradiol, essential for maintaining pregnancy. The definitive cortex surrounds this and is initially thinner. After birth, the foetal cortex begins to disintegrate while the definitive cortex develops. Initially there are only two clear layers to the definitive cortex, but by three years of age the cortex has developed into the three distinct adult layers.

Ectopic adrenal tissue may persist along the site of migration of these two cell layers.

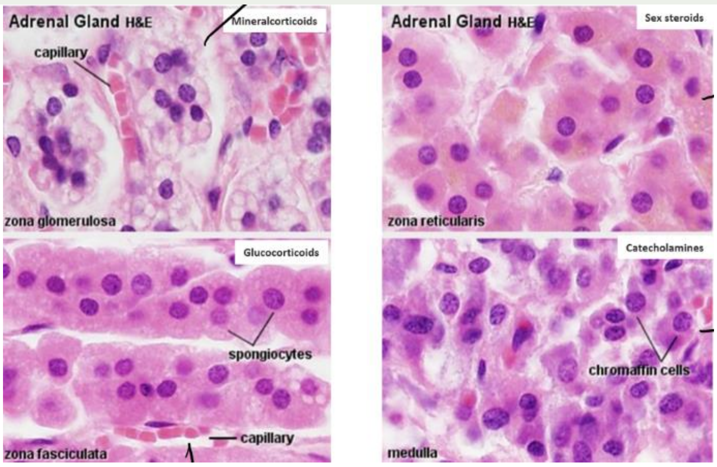
ADRENAL HISTOLOGY

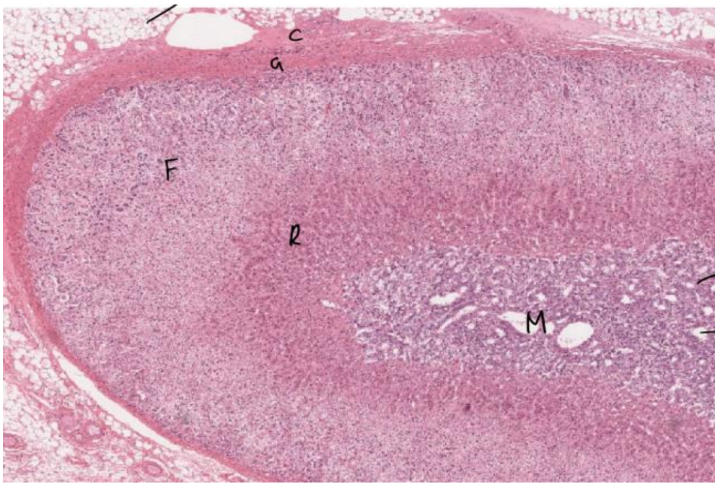
The adrenal gland is composed of distinct layers that have different histological appearances.

The adrenal medulla is composed of chromaffin cells which have a basophilic staining appearance and appear to be less orderly than the cortex. This layer has many glandular structures and is highly vascular. The cytoplasm of the neuronally-derived cells is granular, giving it a more purple appearance on low power. The medulla is responsible for the production of catecholamines. The adrenal gland has an outer capsule that is composed of a thin layer of connective tissue. The cortex of the adrenal gland is also highly vascular.

The adrenal cortex is divided into three layers:

- The zona glomerulosa: This layer contains cells that are arranged into irregular clusters that appear somewhat like glomeruli of the kidney, This is a strongly staining layer and can usually be differentiated from the underlying layer by its stronger colour. The secretory cells here produce mineralocorticoids, particularly aldosterone.
- The zona fasciculata: this layer is responsible for the production of glucocorticoids, primarily cortisol. This layer on high power appears to be arranged into cords of cells, giving it its name derived from fascicle. The cords are often separated by connective tissues. This is the thickest layer of the cortex. It is less darkly staining because of the presence of lipid within the cell.
- The zona reticularis is a disorganised layer that is arranged in a mesh-work way. The cells here are responsible for producing androgens as well as a small number of glucocorticoids. They sometimes stain somewhat brown and have a darkly staining nucleus. The cells of the reticularis on high power appear very eosinophilic.





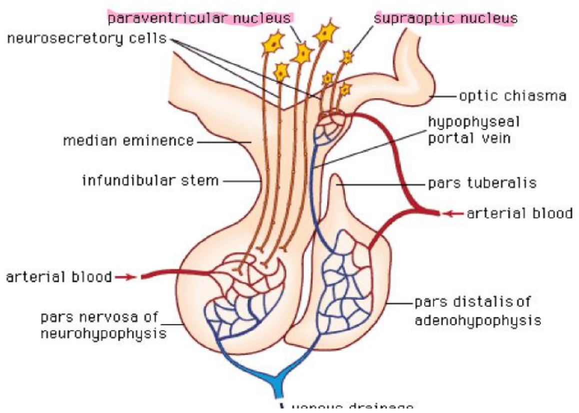
PITUITARY ANATOMY

The pituitary gland is a pea shaped endocrine gland located at the base of the brain, beneath the hypothalamus, to which it is attached via the pituitary stalk or infundibulum. It is composed of two lobes: the adenohypophysis or anterior pituitary and the neurohypophysis or the posterior pituitary.
It is located within the sella turcica, a small depression in the sphenoid bone, (pituitary fossa) of the sphenoid bone inferior to the optic chiasm. It is composed of both an anterior and posterior portion. The gland is covered by the diaphgrama sella (a reflection of dura mater which separates the pituitary from the optic chiasm).
The arterial supply is:

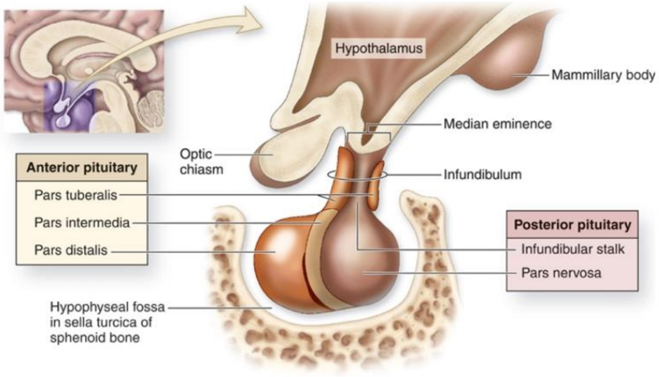
- Superior hypophyseal artery
- Inferior hypophyseal artery

The venous drainage is:

- Hypophyseal vein cavernous sinus



Anteriorly and inferiorly the pituitary is related to the sphenoid sinus, through which it is often surgically accessed. Laterally the pituitary is surrounded by the cavernous sinuses and their contents. The pituitary is also closely related to several key cranial nerves as well as the internal carotid nerves. These relations can have implications for pathology of the pituitary gland.



- The anterior pituitary is connected to the hypothalamus via the hypophyseal portal system of capillaries
    - The anterior pituitary (adenohypophysis) is composed of several glandular endocrine cells arranged in lumps which stain deeply on histology. The cell types responsible for producing different releasing and inhibiting hormones are all mixed together.
        - Chromophobes are lightly staining cells with few secretory granules
        - Acidophils are larger staining cells with eosinophilic appearance and lots of cytoplasm and granules
        - Basophils are larger again, less heavily granulated and purple staining
    - These days the cell types are more common identified using immunohistochemical staining based on hormone production
    - The anterior pituitary is of ectodermal origin
    - The largest part of the anterior pituitary is called the pars distalis of the adenohypophysis
    - The parts intermedia is the intermediate part that sits between the pars distalis and the posterior pituitary and is often very small
    - The pars tuberalis is a component of the anterior pituitary that extends upwards to wrap around the infundibular stem
- The posterior pituitary (neurohypophysis) is connected to the hypothalamus via neuronal axons that run in the pituitary stalk
    - The posterior pituitary is of neuroectoderm origin and has a fibrillary appearance (these are known as pituicytes).
        - These cells are really the ends of neurons whose cell body is located in the lateral walls of the third ventricle
    - The largest part of the inferior pituitary is called the pars nervosa

Type of chromophil	Class	Secretory Product	Target Organ
Acidophil	Somatotrophs (about 50%)	Growth hormone (GH)	General, but a major target is the chondrocytes in epiphyseal growth plates.
	Mammotrophs (about 20%)	Prolactin (PRL)	Milk producing tissue (alveolar cells) in the breast
Basophil	Corticotrophs (about 20%)	Adrenocorticotrophic hormone (ACTH) Melanocyte-stimulating hormone (MSH)	ACTH: corticosteroid cells of the adrenal cortex. MSH: melanocytes
	Thyrotrophs (about 5%)	Thyroid stimulating hormone (TSH)	Thyroid gland
	Gonadotrophs (about 5%)	Gonadotropins: Follicle stimulating hormone (FSH) and Luteinising hormone (LH).	FSH: follicular cells of the ovaries, to promote growth of follicles, or the sertoli cells of the testes to promote spermatogenesis. LH target is developing follicles to promote ovulation, or the Leydig cells of the testes where it promotes secretion of androgens, aiding spermatogenesis.

FEMALE REPRODUCTIVE ANATOMY

The female reproductive tract is located within the pelvic portion of the abdominopelvic cavity. The pelvic cavity is demarcated from the abdominal cavity by the pelvic inlet. The pelvic inlet is composed of:

- Sacral promontory and sacral ala (wings)
- Arcuate line on inner ilium and superior pubic ramus
    - Sometimes the ‘linea terminalis’ is used to describe the pectineal line, arcuate line and sacral promontory
- Pubic symphysis

Below this is also known as the ‘true’ or ‘lesser’ pelvis. The pelvic cavity extends to the pelvic outlet. The pelvic outlet is composed of:

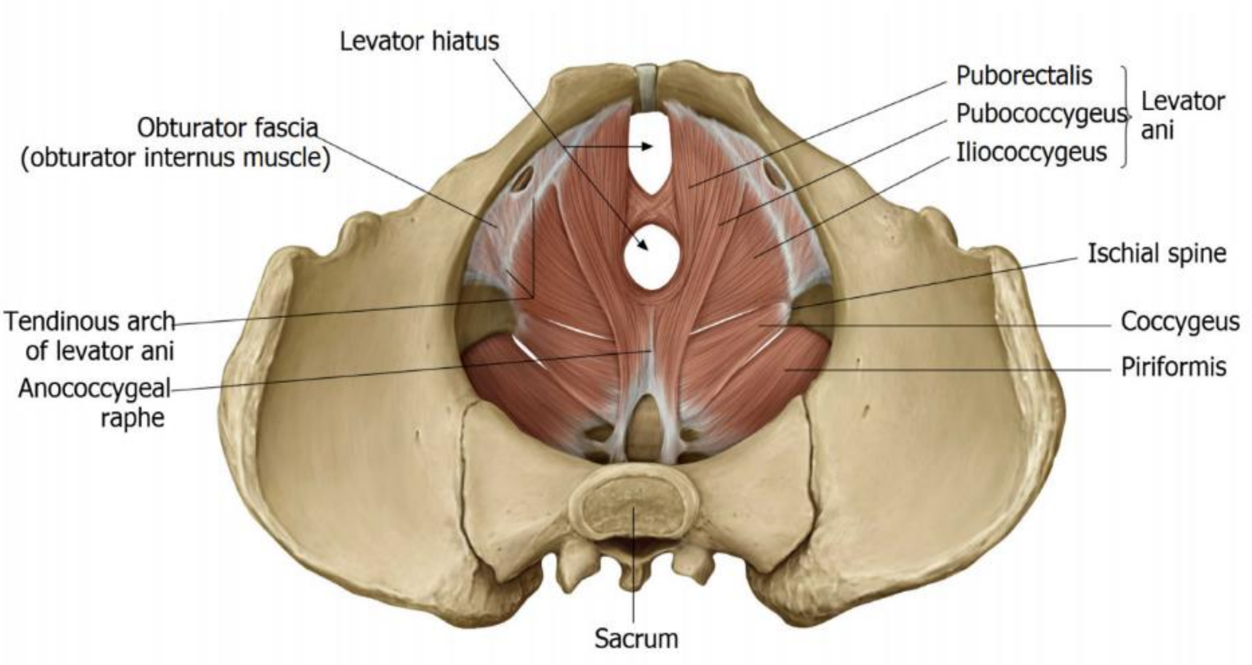
- Tip of the coccyx
- Ischial tuberosities and inferior sacrotuberous ligament
- The pubic arch (inferior border of the ischiopubic rami)

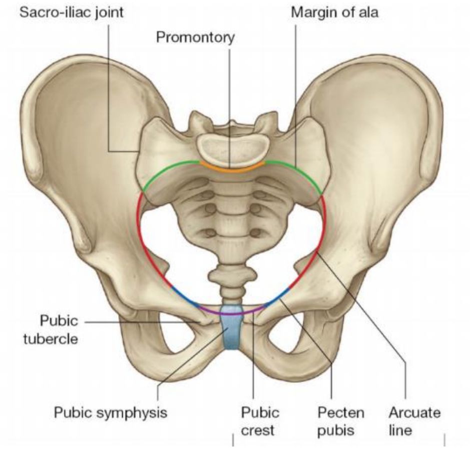
The pelvic diaphragm supports the pelvic organs and separates the pelvic cavity from the outer perineum. It is composed largely of two muscles: the levator ani and the coccygeus. The three components of the levator ani include:

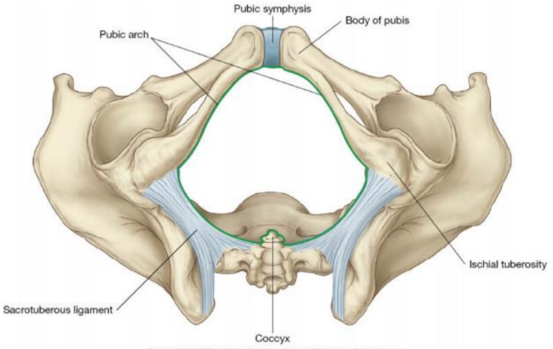
- Puborectalis
    - This is the muscle responsible for maintaining the anorectal angle and maintaining faecal continence
- Pubococcygeus
- Iliococcygeus

Organs that extend to the perineum pass through the pelvic diaphragm via hiatuses in the muscle and fascia. These include the rectal hiatus (most posterior), the vaginal canal and the urethral hiatus. The urethral and the vaginal canal are usually referred to as the urogenital hiatus,

The organs of the female reproductive tract that are in the viscera (above the perineal membrane) are known as the internal genitalia and include the ovaries, uterus and uterine tubes and the vagina.







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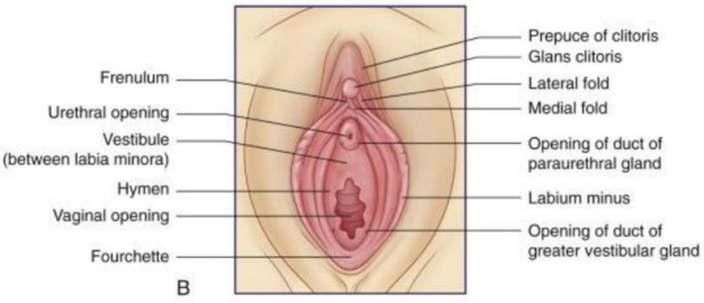
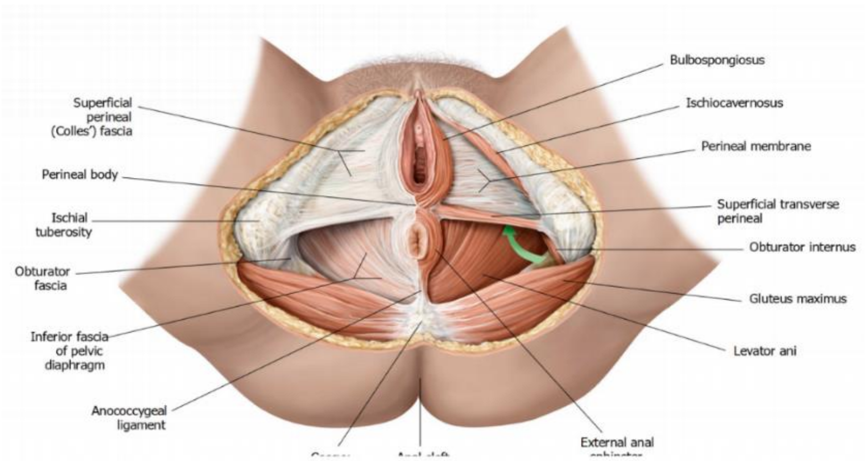
PERINEUM AND EXTERNAL GENITALIA

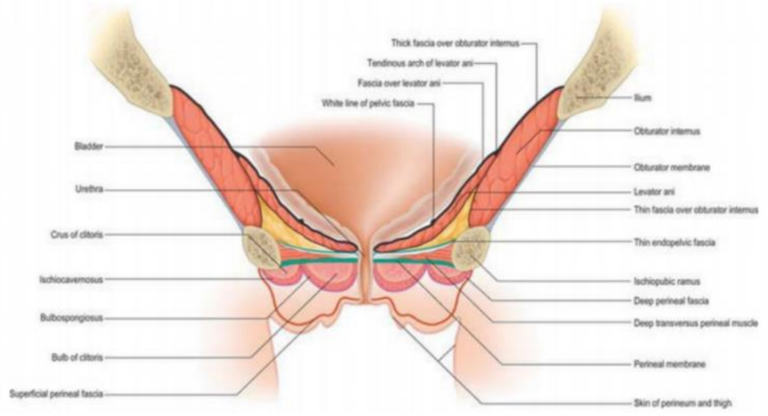
The perineum is the anatomical region located between the thighs, extending from the external skin to the fascia of the pelvic diaphragm. It houses structures of urogenital function. It can be described both in terms of its anatomical boundaries (i.e. the pubic symphysis and the coccyx) or by the surface borders (i.e. the mons pubis, thighs etc.) Both ways of describing the perineum form a diamond shape.

- The anal triangle is the posterior half of the perineum and contains:
    - The anal aperture (located centrally in the triangle)
    - The external anal sphincter muscle
    - Ischioanal fossae
- The urogenital triangle is the anterior half of the perineum and contains:
    - The urethral and vaginal orifices
    - The external genitalia



        - Labia majora: contains fat and the end of the round ligament of the uterus
        - Labia minor: form the prepuce and the frenulum of the clitoris and encloses the vestibule
        - Mons pubis: overlies the pubic symphysis
        - Clitoris: erectile tissue composed of a crura, body and glans
        - Vaginal vestibule: contains external urethral orifice, vaginal orifice, opening of the greater vestibular glands
        - Vestibular bulb: erectile tissue attached anteriorly to the clitoris
        - Greater vestibular glands/Bartholin's glands





The external female genitalia receive somatic nervous supply from many somatic nerves:

- Pudendal nerve
- Ilioinguinal nerve
- Genitofemoral nerve
- Posterior subcutaneous nerve

The cavernous nerves innervate the erectile tissue of the external genitalia.

The female urogenital triangle is composed of multiple pouches formed by layers of fascia. These are known as the deep and superficial perineal pouches. They are separated by the perineal membrane, a layer of strong deep fascia.

- The deep pouch is between the pelvic diaphragm and the perineal membrane
    - Part of the urethra
    - External urethral sphincter
    - Vagina
- The superficial pouch is between the subcutaneous tissue and the perineal membrane
    - Erectile tissues of the clitoris
    - Ischiocavernosus muscle
    - Bulbospongiosus muscle
    - Superficial transverse perineal muscles

The perineal body is a fibromuscular mass located at the junction of the urogenital and anal triangles, making it the centre of the perineum. It connects the muscle fibres of the pelvic floor and the perineum itself. It also helps to act as a tear-resistant body between the vagina and external anal sphincter in women.

The perineum is supplied by the pudendal nerve (S2-S4) and the internal pudendal artery.

- The pudendal nerve exits the pelvis through the greater sciatic foramen
- Enters the perineum through the lesser sciatic foramen and runs in the anterior direction in the pudendal canal

Structures in the pelvis can have pain referred to either above or below a hypothetical line known as the pelvic pain line.

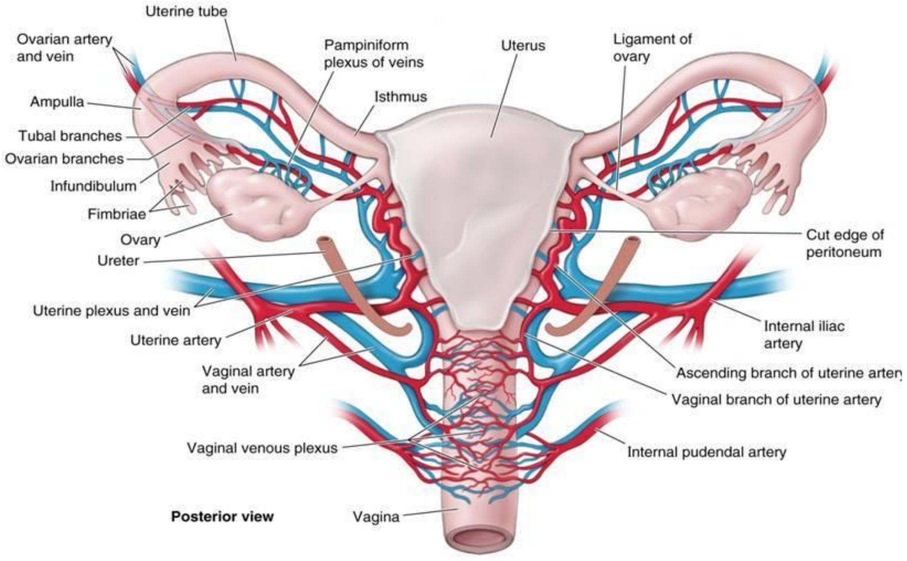
- Structures above the pelvic pain line have referred pain the T10-L1 dermatomes as their pain efferents return to the lower thoracic and upper lumbar levels
- Structures below the pelvic pain line (anything beneath the peritoneum) will have pain referred to the dermatomal segments of S2-S4
    - This area is largely the area corresponding to the perineum and inner thighs

OVARIES

The ovaries are paired organs, connected to the uterus via the uterine tubes. They are almond shape and usually around almond size. They are located on the posterolateral wall of the pelvis in the ovarian fossa between the iliac artery, round ligament and ureters. At birth, their surface is pink and smooth but gradually becomes grey and scarred with development.

They are attached to the posterior surface of the broad ligament of the uterus via a fold of peritoneum known as the mesovarium (attached to the anterior surface). They are also supported by numerous ligaments:

- Suspensory ligaments
    - Extends from mesovarium to pelvic wall
    - This ligament carries the neurovascular bundle supplying the ovaries within it
- Ovarian ligament



        - Extends from ovary to the fundus of uterus

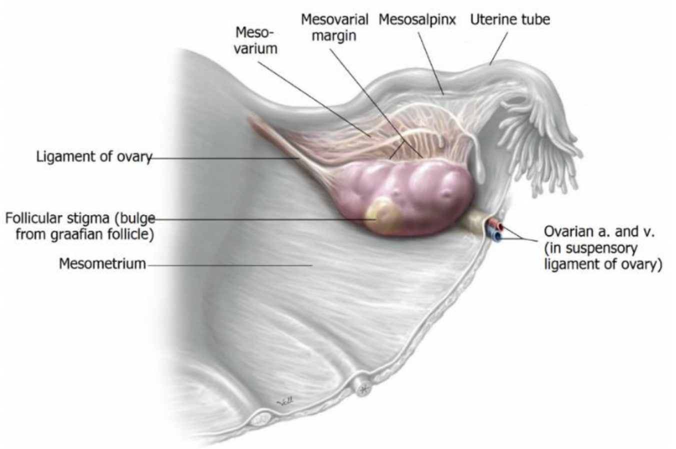
The posterior surface of the ovary that faces the abdominal cavity is covered by a simple cuboidal epithelium through which oocytes are discharged during ovulation.

The ovary has three primary layers:

- The superficial layer of the ovary is a simple cuboidal epithelium
- The cortex of the epithelium is largely composed of connective tissue stroma that supports thousands of primordial follicles. Each follicle is surrounded by a single layer of follicular cells prior to development.
    - Dependant on the ovarian cycle stage, a corpus luteum may also be present
- The medulla of the ovary is composed of supportive stroma and connects the neurovascular network to the outer parts of the ovary

Neurovascular structures of the ovary enter and exit via the suspensory ligament at the hilum of the ovary:

- Ovarian arteries (branches of the abdominal aorta)
- Ovarian veins
    - The ovarian veins form a pampiniform plexus around the ovaries
    - On the left side of the body the ovarian vein drains into the left renal vein
    - On the right side of the body the ovarian vein drains directly into the IVC
- Sympathetic innervation: ovarian plexus
- Parasympathetic innervation: uterine plexus
- Lymphatic drainage from the ovary returns to the paraaortic nodes


Meso-
varium
Mesovarial margin
Mesosalpinx
Uterine tube
Ligament of ovary
Follicular stigma (bulge from graafian follicle)
Mesometrium
Ovarian a. and v. (in suspensory ligament of ovary)

OVARIAN TUBES

The ovarian tubes are embryologically derived from the paramesonephric or Mullerian ducts of the mesoderm. They are also sometimes known as the fallopian tubes, oviducts or uterine tubes.

The ovarian or fallopian tubes connect the peritoneal cavity (where the ovaries are located) to the uterus. They are the site of fertilisation of the ova and responsible for movement of the fertilized ova to the uterus for implantation.

They extend from the wall of the uterus in a superolateral direction, passing superiorly and anteriorly to the ovaries. The ovarian tubes are located within the mesosalpinx of the broad ligament (located on the upper edge of the broad ligament)

The ovarian tubes are divided into four parts:

- The intramural part: located within the myometrium of the uterus
- The isthmus: lateral to the intramural part, a thin narrowing of the uterine tube
- The ampulla: the longest and widest part of the tube in which fertilisation usually takes place
- The infundibulum: the most lateral part of the uterine tube which has a funnel shape and opens into the peritoneal cavity
    - Fimbriae are attached to the infundibulum which are responsible for ‘catching’ the ovulated oocyte and moving them into the ovarian tubes
    - This opening is a site of potential spread for infection into and out of the peritoneum
- The ostium is the site of opening of the uterine tubes into the uterus

The blood supply of the uterine tubes is derived from:

- The uterine artery supplies the medial 2/3
- The ovarian artery supplies the lateral 1/3

The venous drainage of the ovarian tubes consists of:

- The uterine plexus draining the medial 2/3 internal iliac vein
- The pampiniform plexus draining the lateral 1/3 ovarian vein

The lymphatic drainage of the ovarian tubes is to both the paraaortic and the internal iliac lymph nodes.

UTERUS

The uterus is in the midline of the body, posterosuperior to the bladder and anterior to the rectum. The normal anatomical position of the uterus is known as anteverted and anteflexed, meaning rotated and flexed forward towards the front of the body, although it is not uncommon to find uteri that are retroverted and/or retroflexed.

- This positioning predisposes individuals to uterine prolapse.

The angle between the cervix and uterus is known as the angle of anteversion and is usually 90 degrees.

The uterus is the only one of the female reproductive organs that is intraperitoneal.

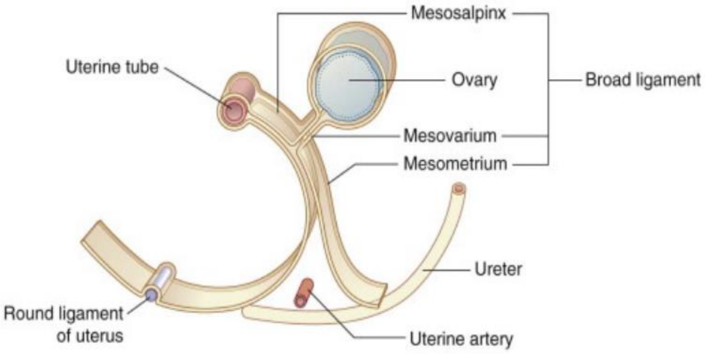
It is composed of three key parts:

- The fundus of the uterus is the top section, located above the uterine tube entry points
- The body of the uterus is the middle section and is the site of implantation in a normal pregnancy
- The cervix of the uterus is the lowest point of the uterus and connects it to the vagina; it is narrower
    - The cervix opens into the vagina, surrounded by fornixes of the vaginal muscle

The uterus is made up of multiple layers:

- It is covered anteriorly by the peritoneum of the abdominal cavity

Sagittal section of broad ligament



- The myometrium is the thick smooth muscle wall of the uterus important in pregnancy
- The endometrium of the uterus is the inner lining of the uterus that undergoes cyclical changes with the monthly cycle of hormones.
    - The stratum basalis is the bottom layer (closest to the myometrium) and changes little throughout the monthly cycle
    - The stratum functionalis is located superficially and undergoes morphological and functional changes throughout the monthly cycle. It is shed during menstruation and re-built throughout the proliferative and secretory phases.

The uterus is supported within the pelvic floor by several key ligaments. These include:

- The broad ligament: this is a double layer of peritoneum that attaches the sides of the uterus to the pelvis, acting as a mesentery and maintaining its positions
- The round ligament: this is a remnant of the gubernaculum that extends from the uterine horns to the labia majora via the inguinal canal and is responsible for maintaining the anteverted position of the uterus
    - This occurs because during embryological development the gubernaculum guides the descent of the ovaries via an attachment to the labia-scrotal swelling
- The ovarian ligament connects the ovaries to the uterus

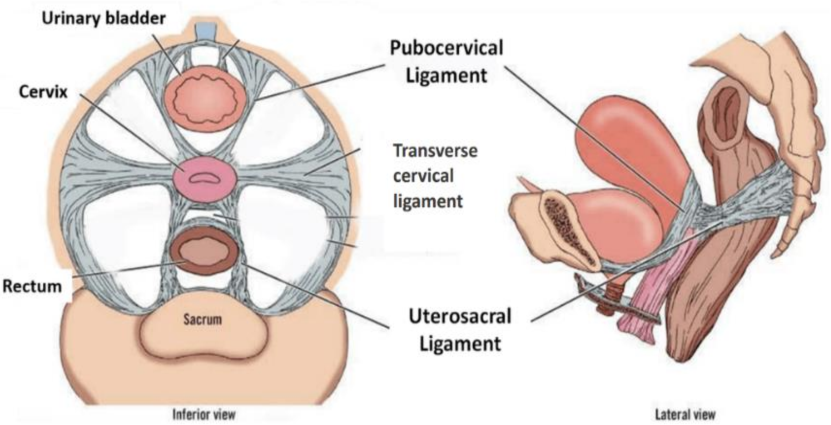
The blood supply to the uterus is derived from the uterine artery, and venous drainage occurs via a plexus of the broad ligament that drains into the uterine veins. The lymph drainage of the uterus is to iliac, sacral, aortic and inguinal lymph nodes.

The uterus is innervated by:

- Parasympathetic fibres of the pelvic splanchnic nerves (s2-4)
- Afferent fibres ascend through the inferior hypogastric plexus to enter the spinal cord at T10-12

The reflections of the peritoneum over the uterus form two clinically relevant pouches of peritoneum in the inferior abdominal cavity. These are:

- The vesicouterine pouch (anterior; between the uterus and the bladder)
- The rectouterine pouch (posterior; between the uterus and the rectum)
    - This is also known as the Pouch of Douglass and is the lowest point of the abdominal cavity within the peritoneum; it is thus a site of fluid collection



VAGINA

The vagina is the connection between the perineum and the uterus and is a distensible muscular tube with several roles including sexual intercourse, childbirth and menstruation. The vagina is located inferior to the uterus, posterior to the bladder and urethra, anterior to the rectouterine pouch, rectum and anal canal and medial to the ureters and levator ani muscle.

The cervix of the uterus extends into the vagina, forming pyramidal shaped fornixes where the cervix and vagina meet, surrounding the external os of the uterus.

At its superior pole, the vagina surrounds the cervix forming what is known as the vaginal fornix.

The arterial supply to the vagina is from:

- Internal iliac artery → The uterine artery
- Internal iliac artery → The vaginal artery

The venous drainage of the vagina occurs via:

- The vaginal venous plexus ▯ uterine vein ▯ internal iliac veins

The lymph drainage of the vagina occurs to:

- The superior portion drains into external iliac nodes
- The middle portion drains into internal iliac nodes
- The inferior portion drains into superficial inguinal nodes

The innervation of the vagina is derived largely from the autonomic nervous system:

- The lower ¼ is somatic
- The upper ¾ is visceral
    - Pudendal nerve
    - Sympathetic: T10/11
    - Parasympathetic: l1/2 via inferior hypogastric plexus

Pelvic Viscera Blood Supply		
Gonadal artery	Branch of abdominal aorta	Pelvic viscera are drained by venous plexuses which drain into the internal iliac vein. These communicate with the vertebral venous plexus.
Uterine artery	Branch of internal iliac artery	
Vaginal artery	Branch of internal iliac artery	

FEMALE REPRODUCTIVE EMBRYOLOGY:

The genetic sex of the female is chromosomally determined at around 8 weeks. The female sex organs are derived from the paramesonephric ducts (Mullerian ducts), while the mesonephric duct (Wolffian duct) degenerates. This occurs when the foetus has XX chromosomes and no SRY gene present. No testes development results in no testosterone, causing the degeneration of the Wolffian or mesonephric duct.

- By week 10 the Mullerian duct develops and descends to become the fallopian tube and the uterus
- The testes develop into ovaries held via the suspensory ligament

The ovaries originate on the posterior abdominal wall and descend to their position in the lower pelvic cavity via the gubernaculum. The gubernaculum is attached to the labia majora in the female. The gubernaculum in females forms the round ligament of the ovary in adults.

- This descent is the reason for the high blood supply origin of the ovarian (gonadal) arteries

BREAST ANATOMY

The normal breast tissue lays superficially to the chest wall and ribs and the pectoralis muscle. The breast is composed of the nipple, the surrounding areola and the breast tissue surrounding this. The breast tissue of the female is more well developed than that of the male.

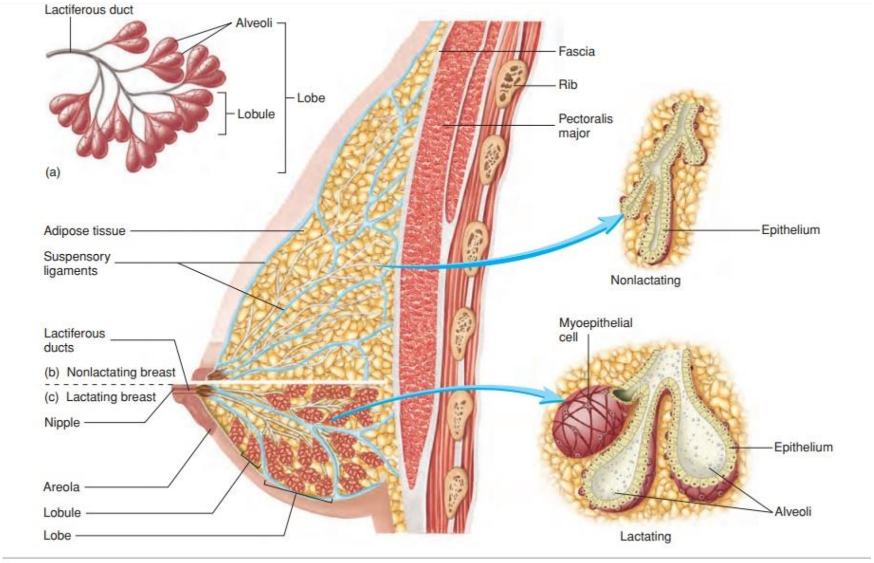


Figure APR **Anatomy of the Breast**

The breast contains mammary glands, consisting of around 15-20 lobules of secretory tissue, connected via ducts. Lobes are divided into lobules, and each of the lobules are composed of many acini. The acini are the 'glands' where the milk is produced.

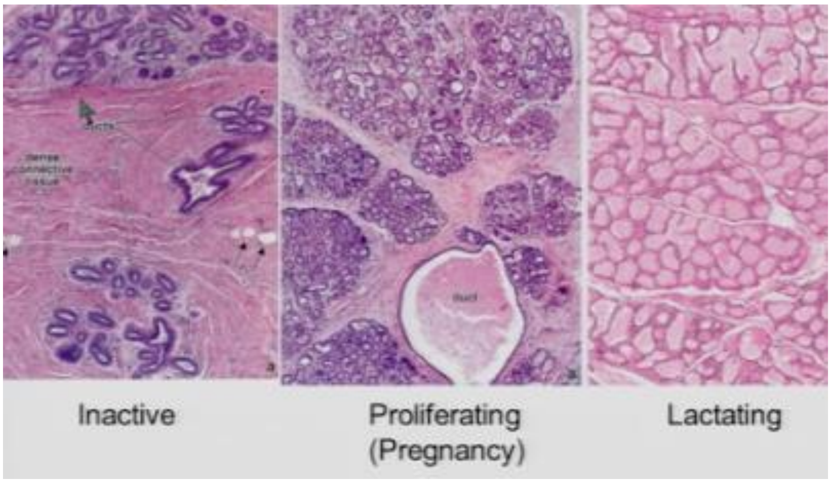
The ducts connecting the system to the final lactiferous duct can be classified as:

- Interlobular or intralobular
- Intralobar or interlobar

The functional unit of the breast is the terminal duct lobular unit or TDLU, composed of the small ducts and acini that compose the terminal unit.

Each acinus is composed of two types of cells surrounding a central lumen.

- Epithelial cells: larger and closed to the lumen
- Myoepithelial cells: smaller, often flattened, with darker nuclei and located exterior to the epithelial cells
    - The presence or absence of myoepithelial cells can be important for diagnosis of pathologies



The breast tissue is supported by connective tissue stroma with both fatty and fibrous components.

- Interlobular stroma surrounds the large ducts and TDLUs
    - Fibrous and collagenous
    - Majority of breast volume
    - Becomes fattier with puberty and post-menopausal
    - Scattered and sparse fibroblasts
- Intralobular stroma
    - Surrounds acini within the TDLY
    - No elastin component
    - Rich is vasculature
    - Contains fibroblasts, lymphocytes, macrophages
    - Responsive to hormones

The composition and appearance of the breast changes with hormonal experiences throughout life.

- An active (fertile) female will have a gland to stroma ratio of around 1:1
- Lactating females will have more glands with very little stroma
    - Lactating breasts will also often be larger and more oedematous
    - The breast tissue may have a frothy appearance due to the milk in the lumen of the breast as well as in the epithelial cells themselves
    - The luminal space is often enlarged
- Atrophic breast tissue can be found in females post-puberty
    - The breast tissue is composed of almost entirely fat

The composition of the male breast is considerably different as testosterone causes involution of the mammary gland. This may show very small and involuted ductal structures (should be very sparse) in a dense matrix of collagenous stroma. There should be very rare or n lobular elements present in the male breast.

The lymph drainage of the breast occurs to the:

- Axillary nodes
    - These are the only palpable breast nodes and are thus very clinically relevant
    - They also drain around 75% of total breast lymph
- Internal mammary nodes
- Supraclavicular nodes
    - These may be palpable in some cases

The arterial supply to the breast is via:

- Axillary artery → lateral thoracic artery
- Posterior intercostal arteries → lateral mammary branches
- Anterior intercostal artery → mammary branch

The venous drainage of the breasts occurs via the:

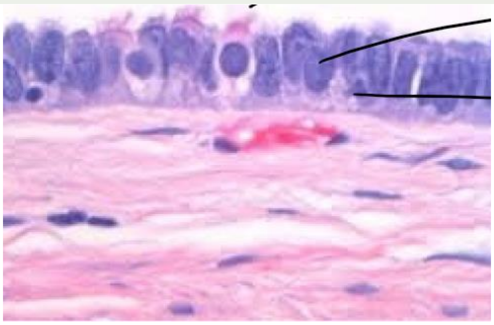
- Axillary veins
- Internal thoracic veins

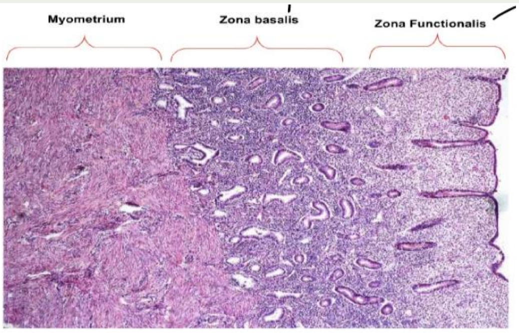
This venous drainage system may anastomose with the vertebral venous plexus, allowing a path for metastasis of breast cancer.

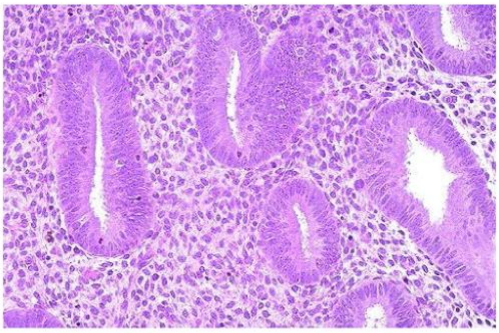
Innervation to the breast is derived from the 4th-6th intercostal nerves.

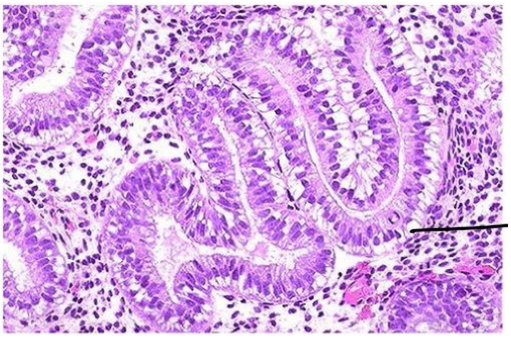
FEMALE REPRODUCTIVE HISTOLOGY:

The uterus is composed of both a muscular myometrium (thick smooth muscle essential for childbirth etc) as well as two layers of endometrium. The myometrium is disorganised in appearance and undergoes hyperplasia and hypertrophy during pregnancy. These layers change throughout the uterine cycle. The innermost layer is the zona or stratum basalis and the outer layer is the stratum or zona functionalis. The outer layer is the layer that is continually shed and rebuilt throughout the cycle. The endometrium tissue is largely glandular with intervening stroma. The glandular appearance and structure changes throughout the cycle too. During the proliferative phase of the cycle, the glands are proliferating and there are increased numbers of mitoses in the gland epithelium as well as the stroma. It appears highly cellular. During the secretory phase, the tissue of the endothelium appears less cellular but there are abundant vacuoles within the glandular epithelium. The glands become more tortuous and there are less mitoses evident. The stroma is less cellular also as stromal oedema increases. During the menstrual phase there is evident blood, with a much pinker stain to the overall tissue. There is shedding and clumping of blood and tissue and neutrophil infiltration into the tissue.









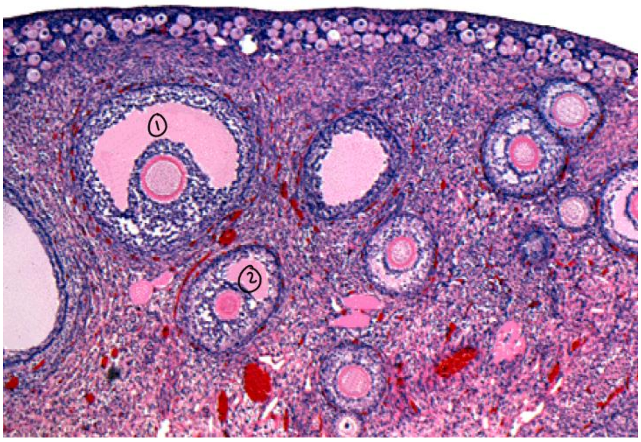
The fallopian tube has evident cilia on top of a lining of columnar appearing cells. Not all of the cells are ciliated, however.

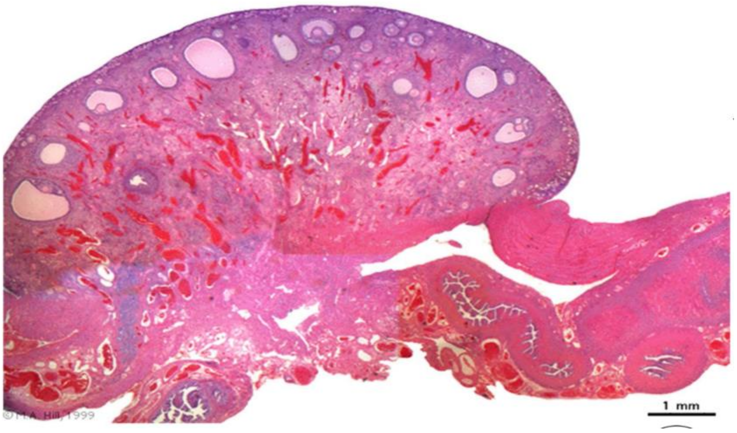
The ovary has an appearance of thin connective tissue stroma surrounding an inner endothelium that appears disorganised and slightly glandular. The surface epithelium of the ovary is a modified mesothelium that has both a layer of flat to cuboidal mesothelial cells. The cortex of the ovary is composed of stroma containing fibroblast-like cells and developing follicles.

- Follicles are composed of a layer of follicular cells surrounding a primary oocyte
- Follicles of differing stages of development can be seen.
    - The primordial follicles are located most superficially and are small, while
    - Primary and secondary follicles have thicker layers of follicular cells and a larger antrum
    - The corpus luteum will have a white/yellow appearance and may be involuted, becoming smaller and whiter.

Stroma comprises the bulk of the ovarian tissue. The medulla of the ovary is composed of fibroblasts, collagen and elastic fibres. It also contains hilar cells that have some androgenic activity. There are visible blood vessels entering at the hilum.

Each of the ovaries contains about 400k primordial follicles containing primary oocytes. The follicles visible in the ovary will be of varying size because they are at varying stages of development. Both the uterine tube and broad ligament may be seen attached to the ovary in low magnification slides.





MALE REPRODUCTIVE ANATOMY

The male reproductive system is composed of the internal and external genitalia responsible for the production and ejaculation of the semen.

Just as in the female, the external genitalia are attached to the perineum, which are divided into an anterior and posterior (or urogenital and anorectal) triangle. These triangles can be divided into two pouches: superficial and deep. Just as in females, the anterior or urogenital triangle is covered by the tough fascia of the perineal membrane, extending between the two sides of the pubic arch and providing attachment points for the genitalia. The key differences in the male are the contents of the deep pouch in males, which includes, alongside the standard contents:

- The membranous urethra
    - There is a hiatus for the urethra in males in the perineal membrane that is not present in females

- The external urethral sphincter
- The bulbourethral glands

The superficial pouch in males, alongside the normal contents, includes:

- The spongy urethra

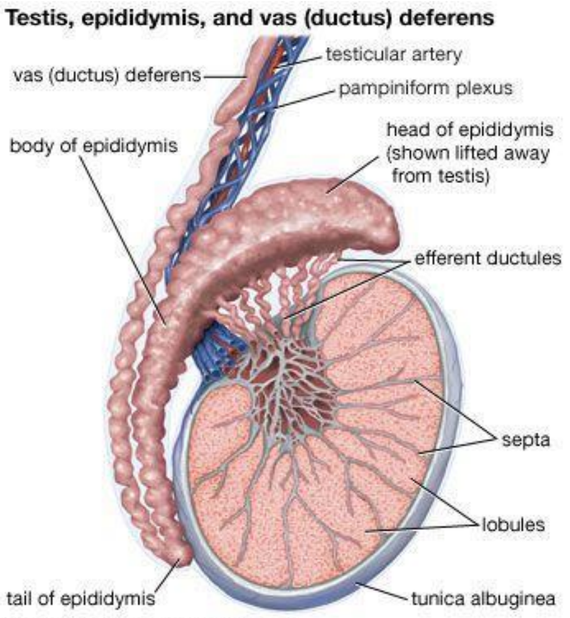
The perineal body is a fibromuscular mass that forms the central tendon of the perineum. It is attached to the posterior aspect of the perineal membrane and provides attachment for many muscles. This is also present in the female.

THE SCROTUM, TESTES AND ASSOCIATED STRUCTURES

The scrotum is a thin-walled sac that extends from the lower anterior abdominal wall, housing the testes which are suspended by the spermatic cord. This is important because it allows for the temperature of the testes to be regulated to maintain optimal spermatogenesis. The skin of the scrotum is continuous with the abdominal wall and perineum. The embryological descent of the testes gives rise to make of the structures in the adult.

The layers of the scrotum include:

- The outer skin (usually covered with hair)
- The dartos muscle
    - This muscle is responsible for creating the wrinkled appearance of the scrotum in order to improve temperature regulation ability
- The external spermatic fascia
    - This is derived from the external oblique fascia of the abdomen
- The cremasteric muscle and fascia
    - This muscle is responsible for allowing the cremasteric reflex (pulling the testes upwards into the abdomen to control temperature of the testes)
    - This is derived from the internal oblique muscle and fascia of the abdomen
- The internal spermatic fascia
    - This is derived from the transversalis fascia of the abdomen



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The testes are surrounded by:

- Spermatic fascia
- Tunica vaginalis
    - Creates a double-layered fluid filled sac around the anterior aspect of the testes to allow for free movement
    - Formed during testicular descent through the peritoneum
    - The tunica albuginea (tough, white capsule)
        - This capsule extends inwards to the testes to divide them into lobules (there are usually between 200-300 septa, each with 3-4 seminiferous tubules)

The testes are composed of numerous seminiferous tubules, in which spermatogenesis occurs. These have a convoluted appearance. They eventually converge at the rete testes, a series of ducts that then converse onto efferent ductules. These are larger ducts and carry the sperm from the rete testes to the head of the epididymis.

The testes receive their arterial supply from:

- The testicular arteries
- Cremasteric artery (branch of inferior epigastric artery)
- Artery of the vas deferens (branch of inferior vesicle artery)

The venous drainage of the testes is via:

- The pampiniform plexus testicular vein renal vein/abdominal aorta
    - The pampiniform plexus also functions in heat exchange for the testes

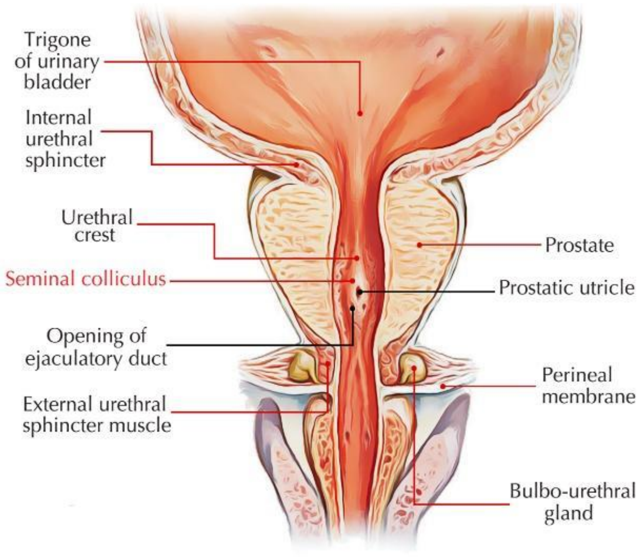
The epididymis sits on the posterior aspect of the testes and is composed of a head, body and tail. It is convoluted in appearance.

- The head is the portion that connects to the efferent tubules
- The body is the largest part that wraps around the inferior aspect of the testes
- The tail is the most distal part that connects to the ductus deferens.

The epididymis is responsible for maturation and storage of spermatozoa.

The ductus deferens is a tube that extends from the tail of the epididymis to join with the seminal vesicles to form the ejaculatory duct. It travels within the posterior aspect of the spermatic cord. It has a thick layer of smooth muscle allowing it to peristaltically move seme forward.

The seminal vesicles are small vesicles located on the posterior surface of the bladder responsible for producing the bulk of the ejaculatory fluid in the form of alkaline fluid. They join the ductus deferens to form the ejaculatory duct.


Trigone of urinary bladder
Internal urethral sphincter
Urethral crest
Seminal colliculus
Opening of ejaculatory duct
External urethral sphincter muscle
Prostate
Prostatic utricle
Perineal membrane
Bulbo-urethral gland

The ejaculatory ducts are formed by the joining of the vas deferens and the seminal vesicles just prior to entry into the prostate gland on the posterior aspect of the bladder. The ducts enter the prostate gland and enter the prostatic urethra through the seminal colliculus (located on either side of the prostatic utricle).

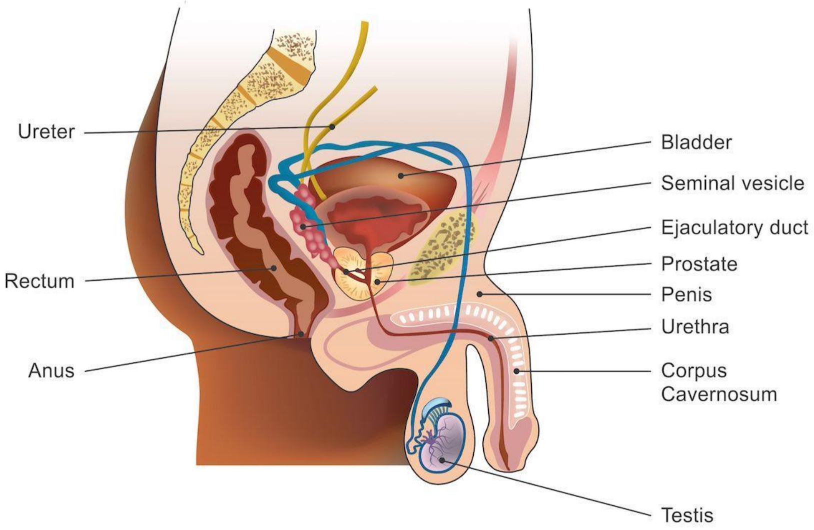
The prostate gland is located immediately inferior to the male bladder (inferior to the internal urethral sphincter) and wraps around the prostatic urethra. It is the site of many openings, allowing fluid for the ejaculate to enter the urethra. The prostate gland itself produces some fluid that contributes to the ejaculate. These openings are largely located in an enlarged section of the prostatic urethra known as the seminal colliculus. The openings include:

- The prostate utricle (this is an embryological remnant of the paramesonephric duct)
- The ejaculatory duct (entry point for the ejaculatory ducts, located medially to the prostatic utricle)

- The prostatic sinuses (entry point for the secretions of the prostate gland, located throughout the prostatic urethra)

The prostate gland itself is a glandular and fibromuscular gland that is surrounded by a strong fibrous tissue capsule. It is divided into multiple zones:

- The transitional zone (located around the prostatic urethra – most common site for BPH)
- The peripheral zone (located inferior and posterior to the transitional zone – most common site of prostatic carcinoma)
- The central zone (located posterior to the anterior zone)



The arterial supply to the prostate comes from the prostatic arteries, largely derived from the internal iliac arteries.

The vasculature of the prostate gland is drained by the prostate plexus of veins, located on its anterolateral surface. These drain into the internal pudendal vein ☐ internal iliac vein ☐ vertebral venous plexus.

- This venous drainage pattern makes the development of vertebral metastases of prostatic carcinoma very common

Just below the prostate gland is the perineal membrane containing the external urethral sphincter and the bulbourethral glands.

These glands are located within the deep perineal pouch and are responsible for the production of alkaline mucus to be mixed with ejaculatory fluid. Their ducts move through the perineal membrane and enter the spongy urethra.

THE URETHRA AND THE PENIS

The male urethra is composed of four parts:

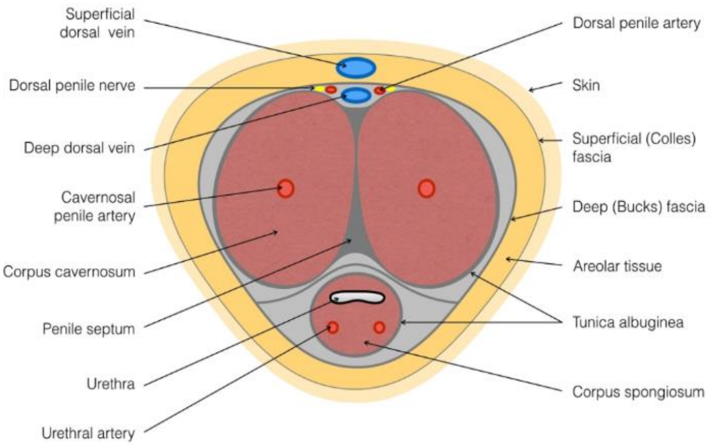
- The intramural part (located in the detrusor muscle of the bladder/aka the pre-prostatic part)
- The prostatic part (surrounded by the transitional zone of the prostate)
- The membranous urethra (surrounded by the external urethral sphincter)
- The spongy urethra (continues to the external urethral orifice)

The penis is composed of three parts:

- The root (the most proximal and fixed part of the penis)
  - The erectile tissues of the penile body extend into the root
    - The corpus cavernosa is known as the two crura
    - The corpus spongiosum is known as the bulb
- The body (the free part of the penis composed of three cylinders of tissue) and is erectile and allows for the ejaculation of semen into the female vagina.
  - Corpus cavernosa (2 bodies, anteriorly)
    - In the root of the penis the extension of this erectile tissue is known as the crura
  - Corpus spongiosum (1 body, posteriorly)
    - This extends at form the glans of the penis
      - The glans contains the navicular fossa of the urethra
    - The spongiosum allows for the spongy urethra to not be too compressed during erection as it remains relatively soft
    - The ridge around the glans of the penis is known as the corona
    - The three erectile tissues of the penis are surrounded by tunica albuginea. This is much thicker around the corpora cavernosa, while it is thinner around the corpus spongiosum.
- The glans (most distal part of the penis formed by distal expansion of corpus spongiosum)
  - Contains the external urethral orifice

The penis is supported by ligaments (i.e. the suspensory ligament and the fundiform ligament) and muscles which include:

- The ischiocavernosus: surrounding the corpora cavernosa
  - These muscles are attached to the ipsilateral ischial rami
  - During an erection, these muscles compress the venous drainage of the penis, allowing it to engorge with blood
- The bulbospongiosus: surrounding the bulb of the penis (x2)
  - The bulb of the penis sits in the midline of the penile root
  - Helps to compress the urethra to ensure all ejaculate and urine are emptied



The arterial supply of the penis is derived from:

- The internal pudendal artery
  - The dorsal artery
    - Skin, fascia, glans
  - The deep artery
    - Corpus cavernosa
  - The artery of the bulb (bulbourethral artery)
    - Bulbourethral glands

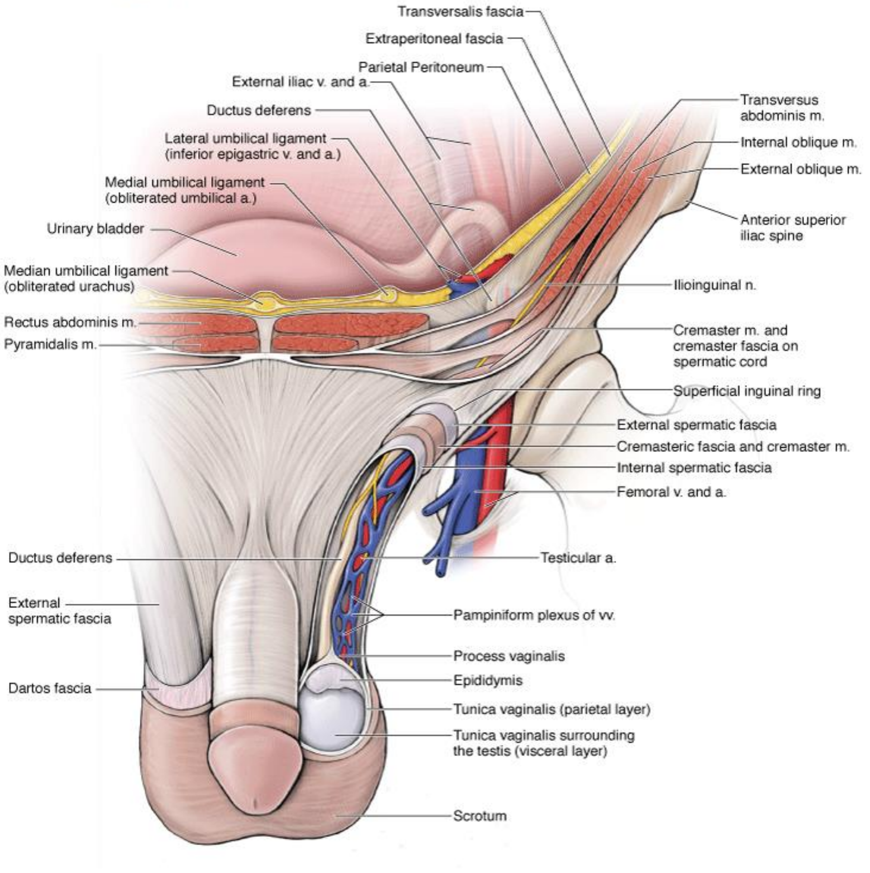
The venous drainage of the penis occurs via the prostatic venous plexus which is derived from the inferior hypogastric plexus. This is drained via:
- The deep dorsal vein
- The superficial dorsal veins

The neural supply of the penis is from:
- The S2-S4 segments.
- It receives sensory innervation as well as sympathetic innervation via the pudendal nerve.
- In addition, the cavernous nerve arises from the prostatic plexus and contain parasympathetic nerves that innervate the helicine arteries of the corpora.

During an erection the following nerves are involved:
- T11-L2 stimulate the smooth muscle in glands and the internal urethral sphincter
    - This sphincter is important to prevent retrograde ejaculation
- The pudendal nerve stimulates the bulbospongiosus muscle in the perineum to compress and cause ejaculation

THE INGUINAL CANAL

The inguinal canal is a canal that extends from the transverse abdominus to the external oblique muscle. It is used for the descent of the testes, as well as other structures that must exit the abdominal cavity. The inguinal ligament extends from the anterior superior iliac spine to the pubic tubercle and is around 4cm long in adults. The inguinal ligament is the structure that marks the location of the inguinal canal, which is a fascial extension from the inferior surface of the external oblique muscle. It is also considered the floor of the canal. The other borders include:
- Anterior: aponeurosis of the external oblique
- Posterior: transversalis fascia
- Roof: transversalis fascia, internal oblique and transversus abdominus
- Floor: inguinal ligament


Transversalis fascia
Extraperitoneal fascia
Parietal Peritoneum
External iliac v. and a.
Ductus deferens
Lateral umbilical ligament (inferior epigastric v. and a.)
Medial umbilical ligament (obliterated umbilical a.)
Urinary bladder
Median umbilical ligament (obliterated urachus)
Rectus abdominis m.
Pyramidalis m.
Transversus abdominis m.
Internal oblique m.
External oblique m.
Anterior superior iliac spine
Ilioinguinal n.
Cremaster m. and cremaster fascia on spermatic cord
Superficial inguinal ring
External spermatic fascia
Cremasteric fascia and cremaster m.
Internal spermatic fascia
Femoral v. and a.
Ductus deferens
Testicular a.
External spermatic fascia
Pampiniform plexus of vv.
Process vaginalis
Epididymis
Dartos fascia
Tunica vaginalis (parietal layer)
Tunica vaginalis surrounding the testis (visceral layer)
Scrotum

Source: Morton DA, Foreman KB, Albertine KH: *The Big Picture: Gross Anatomy:* www.accessmedicine.com
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The entry and exit points of the inguinal canal are:
- The deep/internal ring is in the transversus abdominus muscle
- The outer/superficial inguinal ring is in the external oblique muscle

The inguinal canal contains:
- Spermatic cord (males) contains:
    - Testicular artery
    - Artery to the vas deferens
    - Cremasteric artery
    - Pampiniform plexus
    - Genital branch of the genitofemoral nerve
    - Autonomic nerves
    - Vas deferens
    - Processus vaginalis remnant
    - Lymph vessels
        - Drain into para-aortic lumbar nodes
- Round ligament (females)
- Ilioinguinal nerve

The spermatic cord is composed of:
- External spermatic fascia: deep subcutaneous fascia
- Cremaster muscle and fascia: internal oblique muscle and fascia
- Internal spermatic fascia: transversalis fascia

Summary of male reproductive anatomy innervation:
- Pudendal nerve (S2-S4): somatic nerve that supplies almost all perineal structures
    - Branches to inferior rectal, perineal and dorsal nerve of penis
- Autonomic nerves:
    - SNS T11-L2: Descend from superior hypogastric plexus
    - PNS S2-S4: Travel via pelvic splanchnic nerves to inferior hypogastric plexus
        - Some PNS nerves join prostatic plexus and form cavernous nerves

MALE REPRODUCTIVE HISTOLOGY

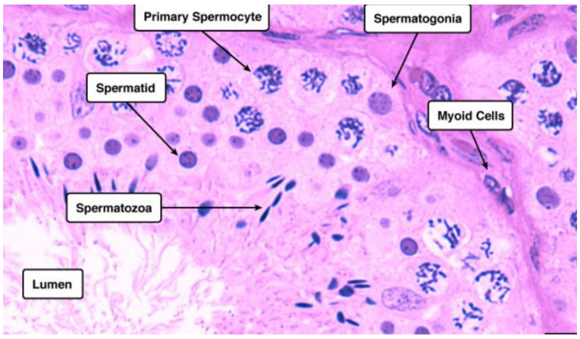
Spermatozoa are produced in and released into the lumen of the seminiferous tubules. The lining of these tubules is composed of Sertoli cells surrounding developing spermatozoa. At the basal layer of the tubule, the spermatogonium reside. As they move further towards the lumen of the cell they become more developed, moving through primary spermatocyte, secondary spermatocyte and spermatid phases before assuming the well known spermatozoa stage. The interstitum of the seminiferous tubules is composed of both myoid cells (which have some contractile ability) and supporting Leydig cells which are eosinophilic and arranged in clusters.

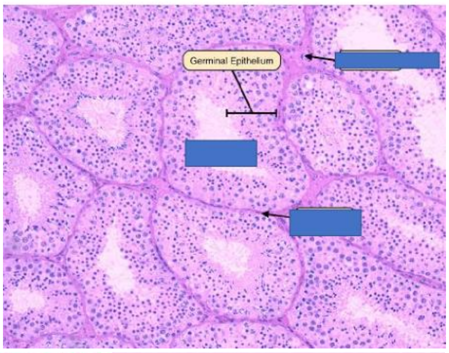
The vas deferens is composed of an inner convoluted lumen surrounded by multiple layers of thick smooth muscle. This is broken into and inner and outer longitudinal smooth muscle layer and a middle circular layer. The epithelial lining of the vas deferens is composed of pseudostratified stereociliated columnar epithelium.

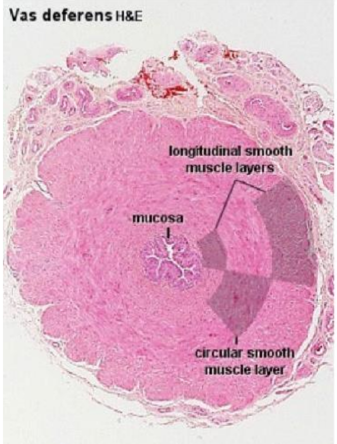
The seminal vesicles have a muscular wall and complex, convoluted mucosal folds surrounding a lumen (i.e. the pink staining top of slide). The cells are pseudostratified ciliated columnar with a prominent basally located nucleus. Below the epithelial layer is a thick layer of smooth muscle responsible for the ejection of seminal fluid.

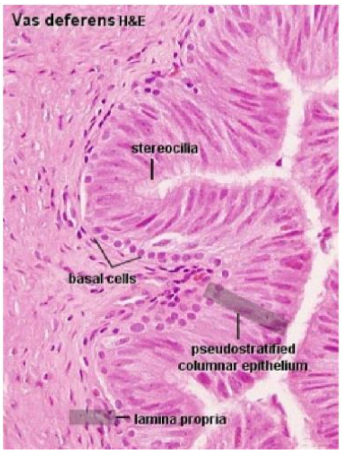
The prostate gland is composed of irregular glandular tissue with fibromuscular stroma between the glands. These glands are usually relatively widely spaced. A reduction in the stroma between glands is usually indicative of pathology. The glandular epithelium of the prostate glands is a single layer of columnar epithelium and a single layer of thin basal cells.

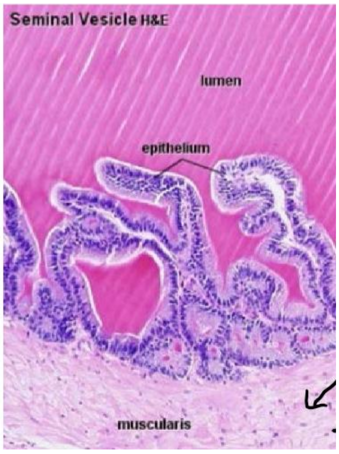
On histology the corpora cavernosa and spongiosum can be seen clearly, as can the convoluted lumen of the penis. This is surrounded by the overlying tunica albuginea connective tissue.

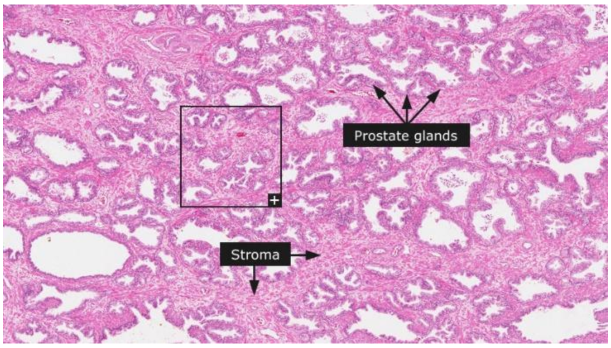


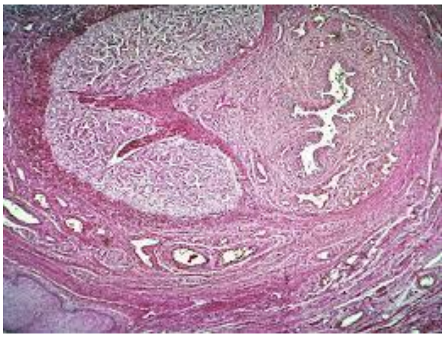



Vas deferens H&E
longitudinal smooth muscle layers
mucosa
circular smooth muscle layer









THYROID & PARATHYROID PHYSIOLOGY

HYPOTHALAMIC-PITUITARY AXIS

The HPA axis is the primary control system for the release of thyroid hormone. This involves the hypothalamus, anterior pituitary and the thyroid gland.

- Small bodies neurons in the arcuate nucleus and median eminence in the hypothalamus synthesize and secrete TRH (thyrotropin releasing hormone) in response to low levels of circulating thyroid hormone
- The TRH moves through the hypophyseal portal system of capillaries to the anterior pituitary
- Thyrotrophic cells in the anterior pituitary respond to the TRH by producing THS (thyroid stimulating hormone) which is released via exocytosis into the circulation
- TSH travels to the thyroid via the circulation and interacts with follicular cells
- Follicular cells respond to TSH in the blood by increasing thyroid hormone production
- Thyroid hormone levels in the blood rise and this has a negative feedback effect on the hypothalamus

THYROID HORMONE SYNTHESIS AND ACTION

Thyroid hormones are synthesized in follicular cells of the thyroid from the precursor thyroglobulin. This is done via the following processes:

- TSH stimulates follicular cells of the thyroid
  - NIS (sodium/iodine transporters) on the basolateral surface of the cell are stimulated to increase iodine uptake into the follicular cell
  - Thyroglobulin production inside the rough endoplasmic reticulum is upregulated via a GPCR 2nd messenger system
  - TSH also stimulates hyperplasia of the thyroid glands
- Iodine is oxidized to Iodide within the follicular cell via thyroperoxidase enzyme
- Thyroglobulin is exported into the colloid of the follicle via endocytosis
- Within the colloid iodination of tyrosine residues on the thyroglobulin occurs
  - This involves the conversion of thyroglobulin into MIT or DIT (one or two thyroid addition)
  - This process is also stimulated by TSH
- Within the colloid conjugation occurs
  - This involves the conjugation of iodinated tyrosine (MIT and DIT) into T4 and T3 linked to thyroglobulin
    - Any T2 is recycled as it is biologically inactive
- The iodinated thyroglobulin is endocytosed into the follicular cells

- The endocytic vesicle binds to intracellular lysosomes
- Proteolysis of the iodinated thyroglobulin occurs, cleaning the thyroglobulin molecule from the T3 and T4
- Secretion of the T4 and T3 are secreted from the cell into the circulation
    - This process is stimulated by TSH

Thyroid hormone is moved through the circulation largely bound to TBG (thyroxine binding globulin). Only free or unbound thyroid hormone is biologically active, thus the bound thyroid hormone provides a pool or reservoir of more hormone for when needed. This pool can usually last around 7 days.

- Substances that affect the levels of circulating TBG (i.e. increased oestrogen during pregnancy) can change the levels of bound thyroid hormone.

When thyroid hormone reaches the target cell, it diffuses through the cell membrane and interacts with intracellular receptors as it is lipid soluble. Deiodinase enzymes remove an extra iodine from the T4 molecule as T3 is more biologically active.

- Deiodinase enzymes (DIO) can be both activating or deactivating.
    - DIO1 is the most common DIO and is present in most tissues throughout the body. It removes an iodine from the outer ring.
    - DIO2 is present in the brain tissue and is central to an important mechanism used during starvation.
        - DIO2 maintains levels of T3 in the brain at normal levels even during starvation, when the rest of the body tissue decreases T4T3 activation. This helps to lower BMR but prevents the hypothalamus from producing excess TRH to compensate.
    - DIO3 is deactivating as it removes an iodine from the inner rin, making it biologically inactive. It is important during foetal development.

There are both nuclear and non-genomic receptors for thyroid hormone within the cell.

PARATHYROID PHYSIOLOGY:

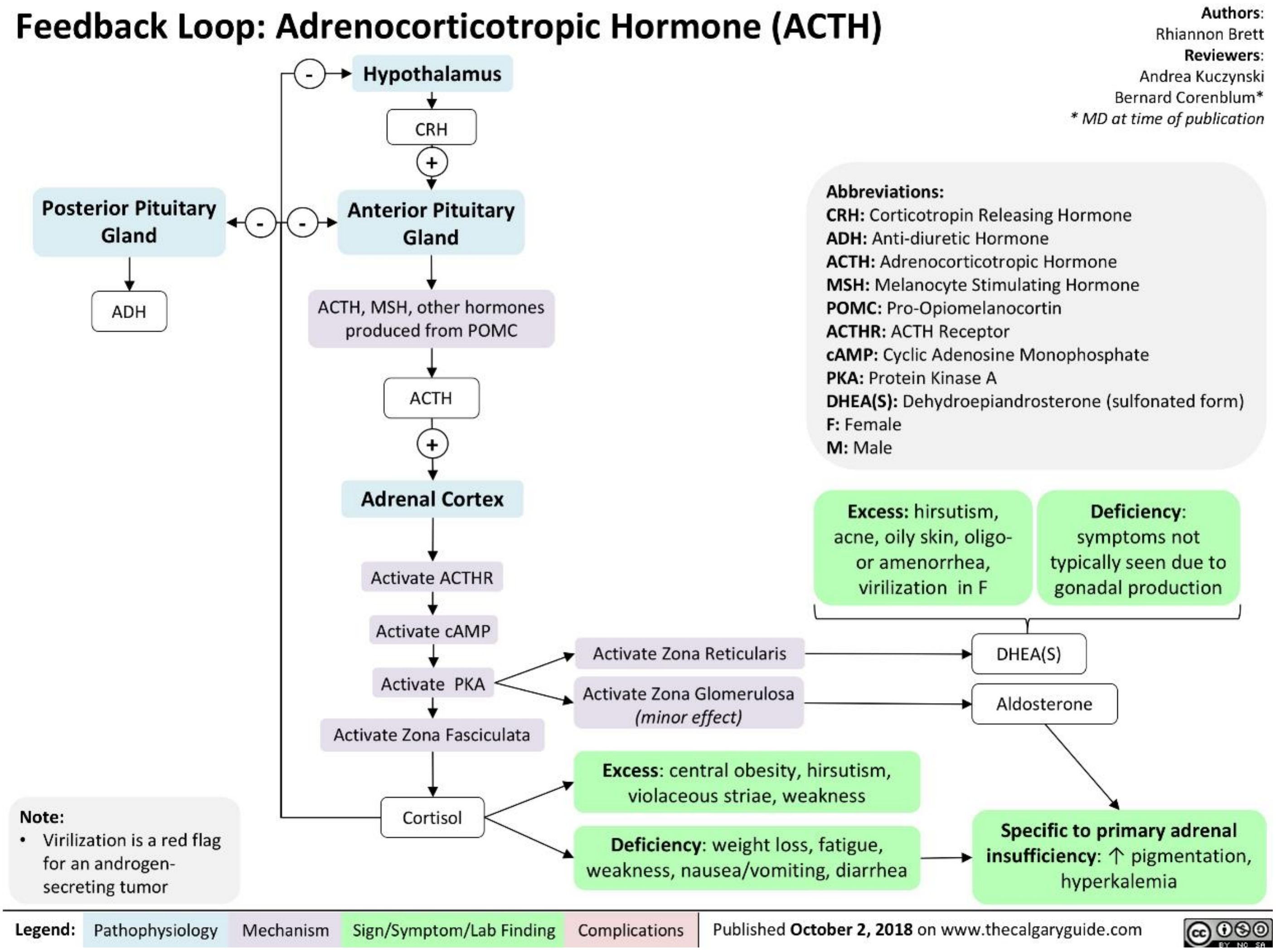
The parathyroid gland produces parathyroid hormone (PTH). It is responsible for maintaining steady serum calcium levels.

- PTH increases:
    - Osteoclast activity (and decreases osteoblast activity) to liberate calcium from bone
    - Vitamin D conversion in the kidney to increase GIT uptake of calcium
    - Kidney retention of calcium and kidney excretion of phosphate

PTH is released when serum calcium levels are low. When serum calcium levels are high, calcitonin is released from the thyroid gland to counteract these mechanisms.

Secondary hyperparathyroidism is a common paraneoplastic syndrome that results in susceptibility to osteoporotic fractures, hypercalcaemia, bone metastasis, and renal stones.

ADRENAL PHYSIOLOGY


Feedback Loop: Adrenocorticotropic Hormone (ACTH)
Authors: Rhiannon Brett
Reviewers: Andrea Kuczynski
Bernard Corenblum*
* MD at time of publication
Hypothalamus
CRH
+
-
Posterior Pituitary Gland
ADH
Anterior Pituitary Gland
ACTH, MSH, other hormones produced from POMC
ACTH
Adrenal Cortex
Activate ACTHR
Activate cAMP
Activate PKA
Activate Zona Reticularis
Activate Zona Glomerulosa (minor effect)
Activate Zona Fasciculata
Cortisol
DHEA(S)
Aldosterone
Abbreviations:
CRH: Corticotropin Releasing Hormone
ADH: Anti-diuretic Hormone
ACTH: Adrenocorticotropic Hormone
MSH: Melanocyte Stimulating Hormone
POMC: Pro-Opiomelanocortin
ACTHR: ACTH Receptor
cAMP: Cyclic Adenosine Monophosphate
PKA: Protein Kinase A
DHEA(S): Dehydroepiandrosterone (sulfonated form)
F: Female
M: Male
Excess: hirsutism, acne, oily skin, oligo- or amenorrhea, virilization in F
Deficiency: symptoms not typically seen due to gonadal production
Excess: central obesity, hirsutism, violaceous striae, weakness
Deficiency: weight loss, fatigue, weakness, nausea/vomiting, diarrhea
Specific to primary adrenal insufficiency: ↑ pigmentation, hyperkalemia
Note:
• Virilization is a red flag for an androgen-secreting tumor
Legend: Pathophysiology Mechanism Sign/Symptom/Lab Finding Complications
Published October 2, 2018 on www.thecalgaryguide.com

The adrenal glands are responsible for producing a number of key hormones in the body. The medulla and the cortex are often thought about separately.

The adrenal medulla is responsible for the production of catecholamines in the blood, largely adrenaline or epinephrine, but is also produces noradrenaline. Due to its neural crest origin, it functions as a post-ganglionic sympathetic neuron and is not controlled like a normal endocrine gland.

- Sympathetic pre-ganglionic fibres run directly to the medulla and produce acetylcholine
- Acetylcholine binds to nicotinic receptors on chromaffin cells of the medulla, initiating a response
- Adrenaline and small amounts of noradrenaline are released into the blood

Adrenaline release from the medulla is largely regulated by the CNS but is also influenced by ACTH and cortisol production to allow for an integrated stress response.

Adrenaline produced by the medulla is usually involved in a stress response or fight/flight response. It works by:

- Increasing blood flow to skeletal muscle
- Relaxing bronchial smooth muscle
- Stimulating lipolysis and glycogenolysis

The cortex is broken into three layers:

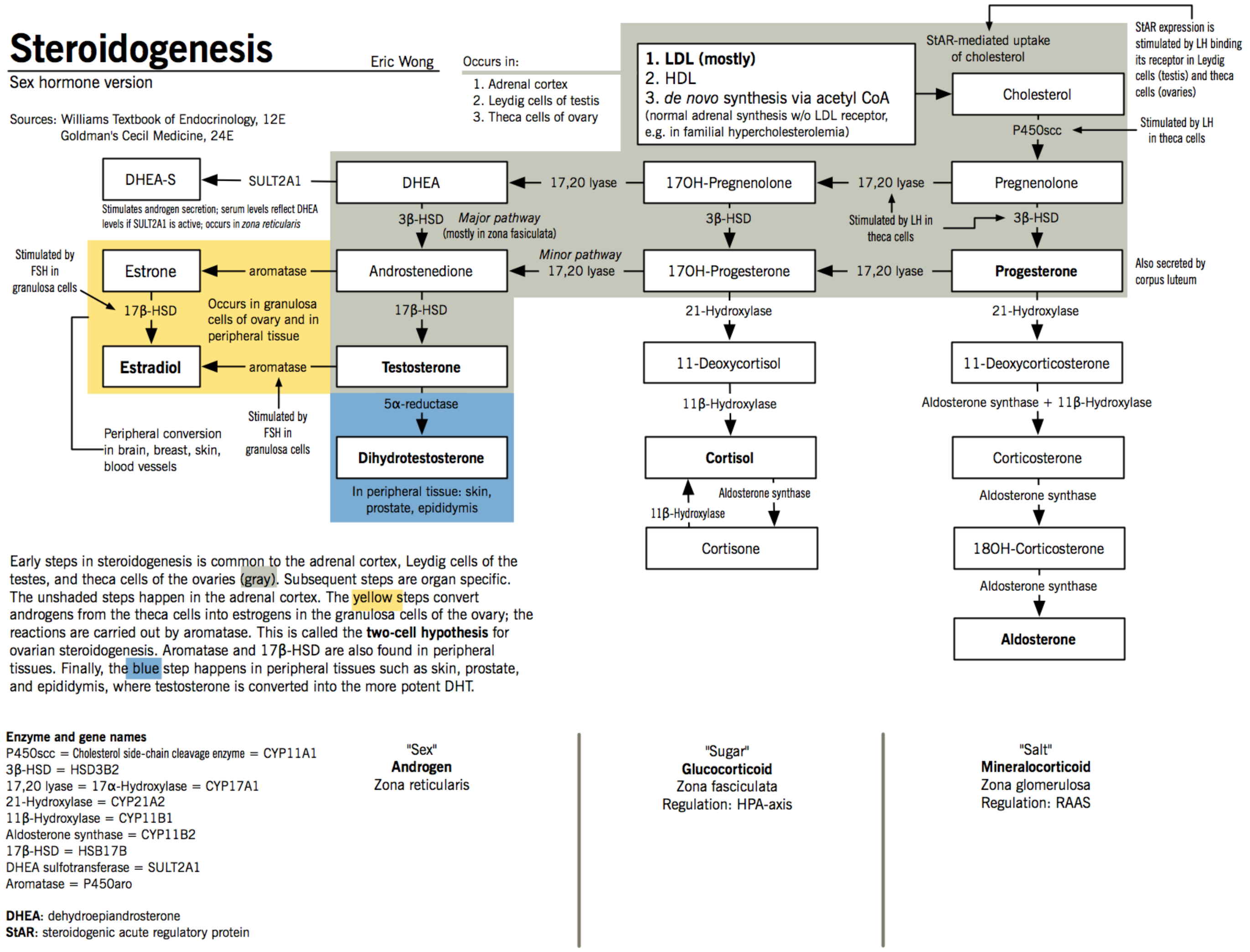
- Zona glomerulosa: produces mineralocorticoids (particularly aldosterone)
  - Regulation of renal sodium and water reabsorption and potassium excretion
  - Controlled largely by the RAAS system
    - Renal hypoperfusion causes the release of renin, which converts angiotensinogen into angiotensin I. Angiotensin I is then converted to angiotensin II by ACE in the lungs, which acts as a vasoconstrictor and stimulates the secretion of aldosterone by the adrenal cortex.
  - Aldosterone binds to the distal tubule kidney cells and causes the insertion of Na/K ATPases which induce the reabsorption of sodium and the secretion of potassium.
  - Aldosterone causes the upregulation of ENaC channels
    - These two effects result in increased sodium and water reabsorption, increased potassium excretion and increased H+ excretion in order to increase blood volume and pressure.
    - Aldosterone also increases H+ excretion from intercalated cells
- Zona fasciculata: produces glucocorticoids (particularly cortisol)
  - Responsible for mobilizing energy reserves during times of stress
  - CRH from the hypothalamus stimulates the secretion of ACTH in the pituitary gland via binding to GPCRs on corticotrophs. This ACTH causes glucocorticoid release in the cortex. CRH is produced by neurons of the paraventricular nucleus and is triggered by pain and stress (which can be both physiological or psychological), pyrogens, hypoglycaemia and hypotension.
    - ACTH in the circulation also binds to melanocortin (MC2) receptors which induces melanocyte activation
    - ACTH also causes some endorphin release, potentially a mechanism for endogenous pain relief
  - Other glucocorticoids have a negative feedback control on CRH release (i.e. exogenous steroids)
  - >90% Cortisol is transported in the body bound to corticosteroid binding globulin (CBG/transcortin)
    - This can be affected by other substances (i.e. increased by oestrogen)
  - CRH and thus cortisol levels have a diurnal rhythm that means cortisol levels are highest in the morning and lowest one hour after sleep
  - Cortisol binds to intracellular receptors
  - Cortisol causes:
    - Gluconeogenesis, glycogen synthesis, protein catabolism, lipolysis, increases appetite and increases insulin resistance
      - Cortisol's metabolic effects mean that in excess it can cause insulin resistance and diabetes, long-term muscle atrophy, skin thinning and inhibition of osteoblasts
    - Increases vascular sensitivity to catecholamines, decreases nitric-oxide mediated vasodilation and maintains BP
      - This has clinical relevance for hypercortisolism conditions
    - Has some immunosuppressive effects (giving rise to its therapeutic use as an anti-inflammatory)
    - Cortisol has permissive effects on catecholamine release in order to create a synergistic response
  - The cortisol-cortisone shunt is important for ensuring that large amounts of cortisol cannot influence the Na+ and K+ balance as mineralocorticoid receptors are responsive to both aldosterone as well as high levels of cortisol
    - 11-b hydroxysteroid dehydrogenase II converts cortisol to cortisone
      - Very high levels of cortisol can overwhelm this enzyme's ability to convert and can activate aldosterone receptors, causing hypertension and hypokalaemia
- Zona reticularis: produces androgens
  - Weak androgens are used as precursors for oestrogen and testosterone
  - These include DHEA and androstenedione
    - Androstenedione is converted into testosterone and then into DHT to increase hair production in androgen sensitive areas, promotes male sexual differentiation, spermatogenesis, increases libido and has anabolic effects.
      - The effects of androgens in women are largely unapparent unless present in excess
      - In adult males DHEA accounts for <5% testosterone production owing to the testicular production of testosterone
    - Oestrogen production from these precursors is important in men and post-menopausal women (but in premenopausal women this is an insignificant source of oestrogen)
    - Oestrogen controls female sexual differentiation during development, pubertal development of secondary sex characteristics, etc.
  - This release is controlled by CRH –> ACTH control but this is not entirely understood as there is no classical feedback system that we know of yet
  - Androgens are important in the development of a baby and this can be seen by their spike during foetal development before a drop off occurs after birth

CATECHOLAMINE SYNTHESIS

Catecholamines are derived from the amino acid tyrosine into noradrenaline and adrenaline in the adrenal gland. Adrenaline is stored in granules in the chromaffin cells and can be released quickly as needed (allowing for the fast flight-flight response).

Catecholamines are removed from the circulation quickly by catecholamine-O-methyltransferase (COMT) and monoamine oxidase (MAO). Because of the short half-life of catecholamines in the blood, the breakdown products metanepherine etc. are often used as measurements of catecholamine activity. Catecholamine synthesis and control relies on important pathways that are often affected by drugs. These include:

- Sympathomimetics: will increase production
- MAO inhibitors: will decrease breakdown
- Norepinephrine and epinephrine reuptake inhibitors will increase levels
- Adrenergic-receptor blockers will decrease activity



Steroidogenesis

Sex hormone version

Eric Wong

Sources: Williams Textbook of Endocrinology, 12E
Goldman's Cecil Medicine, 24E

Occurs in:
1. Adrenal cortex
2. Leydig cells of testis
3. Theca cells of ovary

1. LDL (mostly)
2. HDL
3. de novo synthesis via acetyl CoA
(normal adrenal synthesis w/o LDL receptor, e.g. in familial hypercholesterolemia)
StAR-mediated uptake of cholesterol
StAR expression is stimulated by LH binding its receptor in Leydig cells (testis) and theca cells (ovaries)
Cholesterol
P450scc
Stimulated by LH in theca cells
DHEA-S
SULT2A1
Stimulates androgen secretion; serum levels reflect DHEA levels if SULT2A1 is active; occurs in zona reticularis
DHEA
17,20 lyase
17OH-Pregnenolone
17,20 lyase
Pregnenolone
3β-HSD
Major pathway (mostly in zona fasiculata)
3β-HSD
Stimulated by LH in theca cells
3β-HSD
Stimulated by FSH in granulosa cells
Estrone
aromatase
Androstenedione
Minor pathway 17,20 lyase
17OH-Progesterone
17,20 lyase
Progesterone
Also secreted by corpus luteum
17β-HSD
Occurs in granulosa cells of ovary and in peripheral tissue
17β-HSD
21-Hydroxylase
21-Hydroxylase
Estradiol
aromatase
Testosterone
11-Deoxycortisol
11-Deoxycorticosterone
Stimulated by FSH in granulosa cells
5α-reductase
11β-Hydroxylase
Aldosterone synthase + 11β-Hydroxylase
Peripheral conversion in brain, breast, skin, blood vessels
Dihydrotestosterone
In peripheral tissue: skin, prostate, epididymis
Cortisol
Corticosterone
Aldosterone synthase
11β-Hydroxylase
Aldosterone synthase
Cortisone
18OH-Corticosterone
Aldosterone synthase
Aldosterone

Early steps in steroidogenesis is common to the adrenal cortex, Leydig cells of the testes, and theca cells of the ovaries (gray). Subsequent steps are organ specific. The unshaded steps happen in the adrenal cortex. The yellow steps convert androgens from the theca cells into estrogens in the granulosa cells of the ovary; the reactions are carried out by aromatase. This is called the **two-cell hypothesis** for ovarian steroidogenesis. Aromatase and 17β-HSD are also found in peripheral tissues. Finally, the blue step happens in peripheral tissues such as skin, prostate, and epididymis, where testosterone is converted into the more potent DHT.

Enzyme and gene names
P450scc = Cholesterol side-chain cleavage enzyme = CYP11A1
3β-HSD = HSD3B2
17,20 lyase = 17α-Hydroxylase = CYP17A1
21-Hydroxylase = CYP21A2
11β-Hydroxylase = CYP11B1
Aldosterone synthase = CYP11B2
17β-HSD = HSB17B
DHEA sulfotransferase = SULT2A1
Aromatase = P450aro

DHEA: dehydroepiandrosterone
StAR: steroidogenic acute regulatory protein

"Sex"	"Sugar"	"Salt"
Androgen	**Glucocorticoid**	**Mineralocorticoid**
Zona reticularis	Zona fasciculata	Zona glomerulosa
	Regulation: HPA-axis	Regulation: RAAS

CORTEX HORMONE SYNTHESIS:

Cortex hormones are all steroids. They are derived from a cholesterol precursor, which can be derived from either endogenous or exogenous cholesterol sources, although exogenous sources are believed to be more important. The different regions of the cortex contain different enzymes able to process the precursor molecules into different hormones, giving them their functional independency.

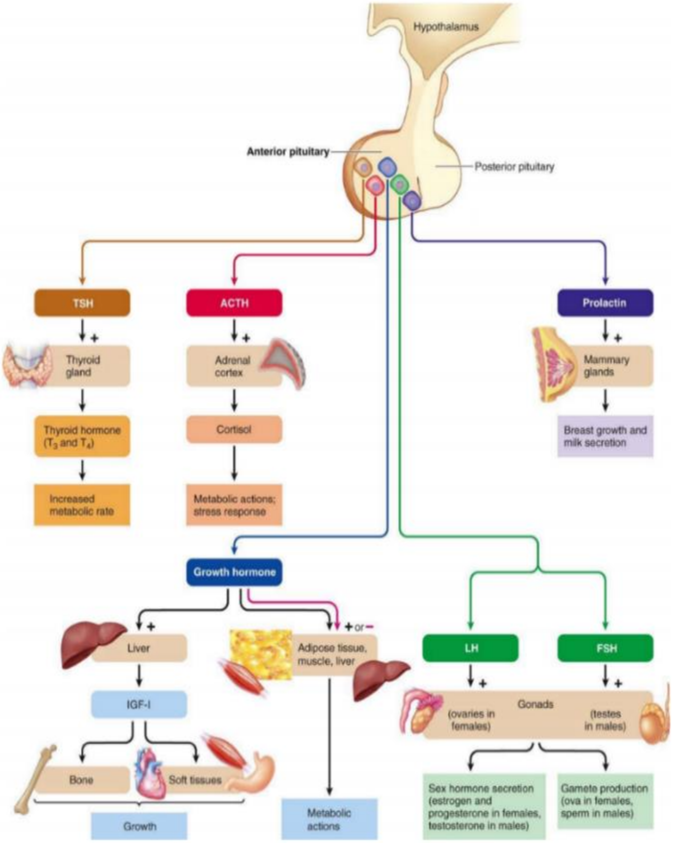
- ACTH stimulates cholesterol to be taken up by the adrenal cortex mitochondria
- Side chain cleavage enzymes turn cholesterol in pregnenolone in the zona glomerulosa
    - Pregnenolone □ 17-a hydroxylase □ 17-hydroxypregnenolone (zona fasciculata)
        - 17-hydroxypregnenolone □ 17-a hydroxylase □ 17-hydroxyprogesterone (zona fasciculata)
        - 17-hydroxypregnenolone □ 17-20 desmolase □ DHEA
            - DHEA □ androstenedione (zona reticularis)
            - Androstenedione □ testosterone □ 5a reductase □ DHT
            - Androstenedione □ testosterone □ aromatase □ oestradiol
- Pregnenolone can be formed into progesterone in the zona glomerulosa
    - Progesterone □ 17-a hydroxylase □ 17-hydroxyprogesterone (zona fasciculata)
        - 17-hydroxyprogesterone □ 17,20-desmolase □ androstenedione
        - 17-hydroxyprogesterone □ 21-hydroxylase □ 11-deoxycortisol
            - 11-deoxycortisol □ 11b-hydroxylase □ cortisol (zona fasciculata)
            - Cortisol □ 11b-hydroxysteroidhydrogenase □ cortisone
    - Progesterone □ 21 hydroxylase □ 11-dehydroxycorticosteroid (zona glomerulosa)
        - 11-dehydroxycorticosteroid □ aldosterone synthase □ aldosterone (zona glomerulosa)
        - 11-dehydroxycortidosteroid □ 17a hydroxylase □ 11-deoxycortisol
            - 11-deoxycortisol □ 11bhydroxylase □ cortisol
            - Cortisol □ 11b-hydroxysteroiddehydrogenase □ cortisone (zona fasciculata)

When one pathway of development cannot be completed (i.e. because of enzyme insufficiency) all precursors will progress through alternate pathways. This causes deficiencies of some hormones and excesses in others. Key examples of this include:

- 17a hydroxylase deficiency causes:
  - Increased mineralocorticoid levels,
  - Decreased cortisol
  - Decreased sex hormones
  - Increased BP and
  - Increased ACTH
- 21a hydroxylase deficiency causes:
  - Decreased mineralocorticoid levels, Decreased cortisol levels
  - Increased sex hormone levels
  - Decreased BP and
  - Increased ACTH
- 11b hydroxylase deficiency causes:
  - Increased mineralocorticoids
  - Decreased cortisol
  - Increased sex hormones
  - Increased BP and
  - Increased ACTH
    - This is because 11-deoxycortisol (11-DOC) can act as a weaker version of aldosterone

PITUITARY PHYSIOLOGY

The pituitary gland is a core component of the HPA axis.


Hypothalamus
Anterior pituitary
Posterior pituitary
TSH
+
Thyroid gland
Thyroid hormone (T_3 and T_4)
Increased metabolic rate
ACTH
+
Adrenal cortex
Cortisol
Metabolic actions; stress response
Prolactin
+
Mammary glands
Breast growth and milk secretion
Growth hormone
+
Liver
IGF-I
Bone
Soft tissues
Growth
+ or −
Adipose tissue, muscle, liver
Metabolic actions
LH
FSH
+
+
Gonads
(ovaries in females)
(testes in males)
Sex hormone secretion (estrogen and progesterone in females, testosterone in males)
Gamete production (ova in females, sperm in males)

The posterior pituitary stores and releases hormones produced in the neurons located in the hypothalamus:

- Oxytocin: causes uterine contraction and a milk release reflex
- ADH: has anti-diuretic and water-conserving activity
  - Responsible to plasma osmolality as well as circulating blood volume

The anterior pituitary gland produces the following hormones in response to hypothalamic releasing hormones:

- LH: stimulates Leydig cell testosterone production in men and E2 and progesterone production in women
- FSH: stimulates Sertoli cell spermatogenesis in men and follicular development in women
- GH: causes the production of IGF-1 and is involved in control of growth and development
- TSH: causes the production and release of thyroid hormones
- ACTH: causes the production and release of cortisol
- Dopamine: inhibits prolactin release
- Somatostatin: inhibits GH and TSH release

A basic pituitary investigative pain involves looking at:

- TSH and T4 (can also check T3)
- ACTH and cortisol (can also check blood sugar levels as high cortisol will result in hyperglycaemia)
- GH and IGF-1: GH has a short half-life making its product IGF-1 more clinically useful
- FSH and LH: oestrogen and testosterone
  - Can also check serum sex binding globulin
- Urea and electrolytes
- Serum osmolarity
- Urine osmolarity
- Prolactin and macroprolactin

Interpreting a pituitary panel involves looking at both the pituitary hormone and the end-organ hormone.

	Pituitary Hormone Elevated	**Pituitary Hormone Normal**	**Pituitary Hormone Low**
End-organ hormone elevated	Pituitary-OMA	Lab error Hormone replacement	Primary end organ overactivity Hormone replacement
End-organ hormone normal	End organ becoming lazy Subclinical hypo-activity	Normal	Mild primary organ overactivity Hormone replacement Subclinical hyper-activity
End-organ hormone low	Endocrine organ failure	Relative hypopituitarism	Hypopituitarism

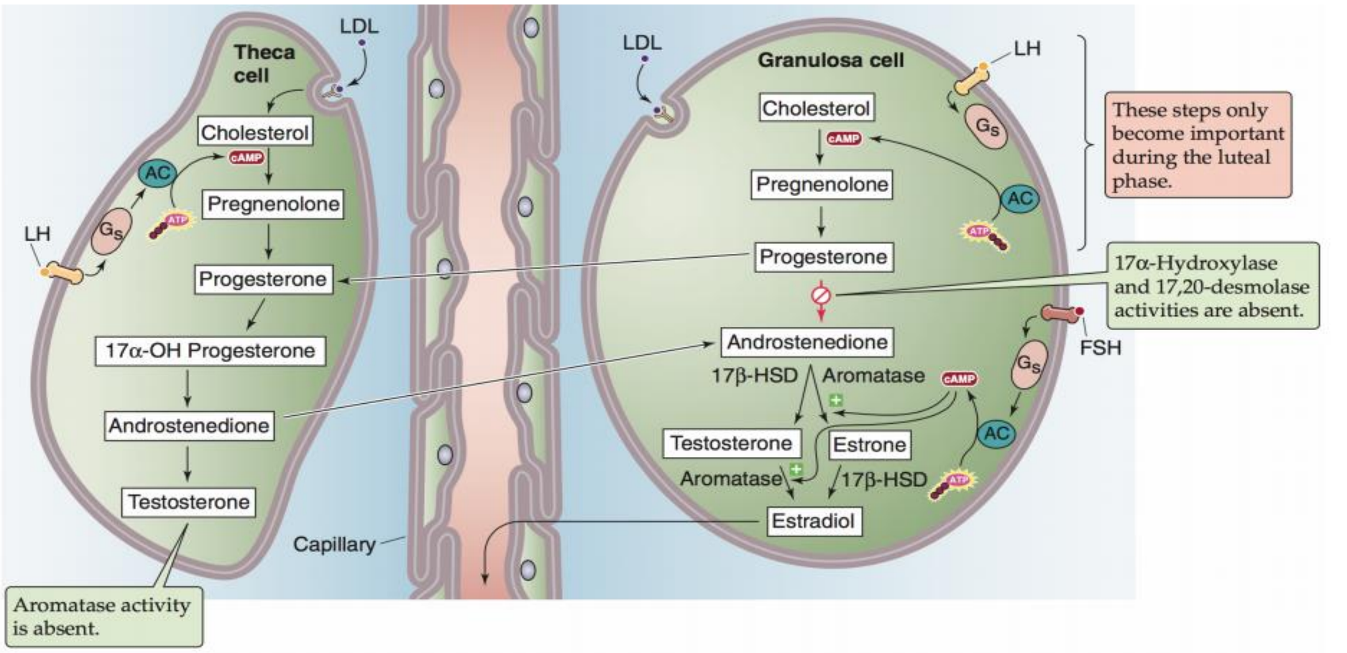
FEMALE REPRODUCTIVE PHYSIOLOGY

The female reproductive system is controlled by the hypothalamus-pituitary-ovarian axis. It is more complicated than a standard negative feedback system because of the impacts of hormone-secreting structures that are formed and degenerate throughout the monthly cycle.

The standard female cycle (ovarian and uterine) is considered to be 28 days long, but this is highly variable between women. The cycle consists of menstruation, ovulation and preparation for implantation of an embryo, If there is no implantation, the cycle begins again.

The two cell types of the developing follicle, the thecal and the granulosa cells, work together to produce sex hormones. This is known as the two cell, two gonadotrophin molecule model. The granulosa cells are on the inner layer and thus closer to the oocyte, while the thecal cells are on the outer layer and further away.

- Thecal cells respond largely to LH to stimulate steroid synthesis
    - Thecal cells produce testosterone and androstenedione
    - They do this from both cholesterol precursors and progesterone
        - Progesterone is sourced from the granulosa cells
- Testosterone and androstenedione are moved from the thecal cells into the granulosa cells which converts them into oestrogen
    - This is important because the granulosa cells do not have the 17a-hydroxylase enzyme required for the conversion of progesterone into androstenedione, and the thecal cells do not have the aromatase enzyme necessary for the conversion of weak androgens into oestradiol
- Granulosa cells are particularly responsive to FSH

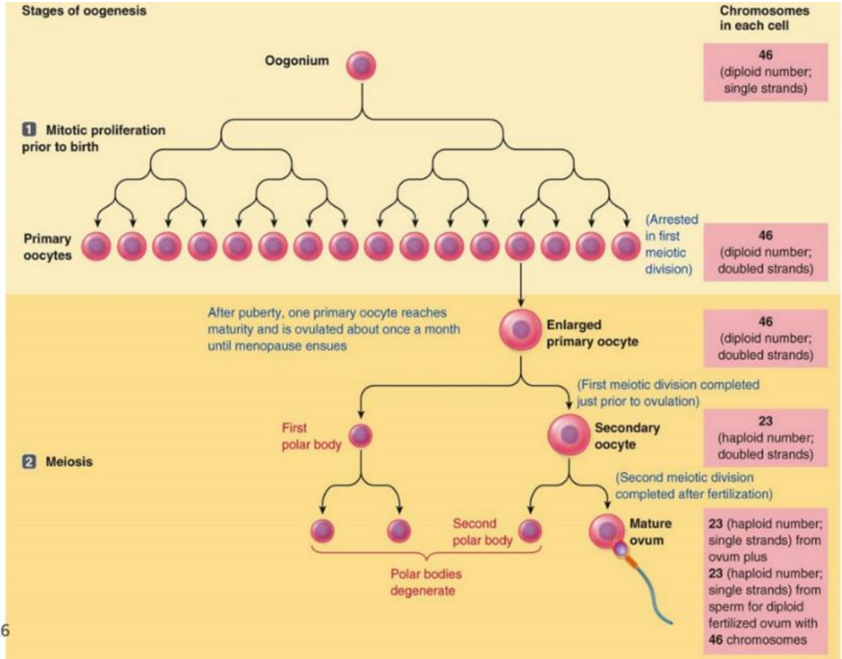


OOCYTE DEVELOPMENT

The oocyte is the female reproductive cell. A female baby is born with all of the oocytes she will have in her life, all contained within the cortex of the two ovaries. They are arrested in the first meiotic division at birth and remain in arrest until the female enters puberty. These are known as primordial follicles and are surrounded by a layer of precursor granulosa cells.

After puberty, primary oocytes complete meiosis I to produce a secondary oocyte under the influence of hormones. There are usually multiple primary oocytes recruited during this phase, but eventually only one (sometimes two) oocytes become dominant.

- The completion of meiosis I results in the formation of one polar body and one secondary oocyte
    - This occurs to ensure the final ovum has a large cytoplasm
    - The first polar body may or may not undergo a second division, but both of the daughter cells are atrophied
- The secondary oocyte is ovulated and meiosis II resumes
    - The secondary oocyte is haploid
    - The secondary oocyte does not complete meiosis II until fertilisation occurs


Stages of oogenesis
Chromosomes in each cell
Oogonium
46 (diploid number; single strands)
1 Mitotic proliferation prior to birth
Primary oocytes
(Arrested in first meiotic division)
46 (diploid number; doubled strands)
After puberty, one primary oocyte reaches maturity and is ovulated about once a month until menopause ensues
Enlarged primary oocyte
46 (diploid number; doubled strands)
(First meiotic division completed just prior to ovulation)
First polar body
Secondary oocyte
23 (haploid number; doubled strands)
2 Meiosis
(Second meiotic division completed after fertilization)
Second polar body
Mature ovum
Polar bodies degenerate
23 (haploid number; single strands) from ovum plus 23 (haploid number; single strands) from sperm for diploid fertilized ovum with 46 chromosomes

The development occurs in the following stages:

- Primordial germ cells migrate from hindgut to gonadal ridge
- Oogonium proliferate via mitosis in the ovary
- At 8 weeks gestation, oogonia enter meiosis I
- Oogonia become primary oocytes
- Meiotic arrest occurs
- At puberty the primary oocytes are surrounded by pre-granulosa cells (primordial follicle)
- Primordial follicles become primary follicles when pre-granulosa cells become granulosa cells
    - A primary follicle is a primary oocyte surrounded by a single layer of granulosa cells

- The zona pellucida forms and granulosa cells proliferate around the oocyte
- Theca cells differentiate and form the preantral follicle
- Follicles are recruited under the influence of FSH (beginning of the monthly cycle)
- Antrum continues to expand developing into a secondary follicle
- The tertiary/antral follicle is formed as the granulosa cells increase and zona pellucida is formed
- The Graafian follicle is formed as the antrum enlarges and the cumulus attaches the oocyte to the rest of the follicle
- The dominant follicle is recruited by increased estrogen levels and continues to proliferate
- Less dominant follicles undergo atresia
- Ovulation occurs and dominant ovum leaves the follicle

OVARIAN CYCLE

The ovarian cycle refers to the process that leads to the development and ovulation of a secondary oocyte as well as the surrounding follicle. The steps occur in two phases.

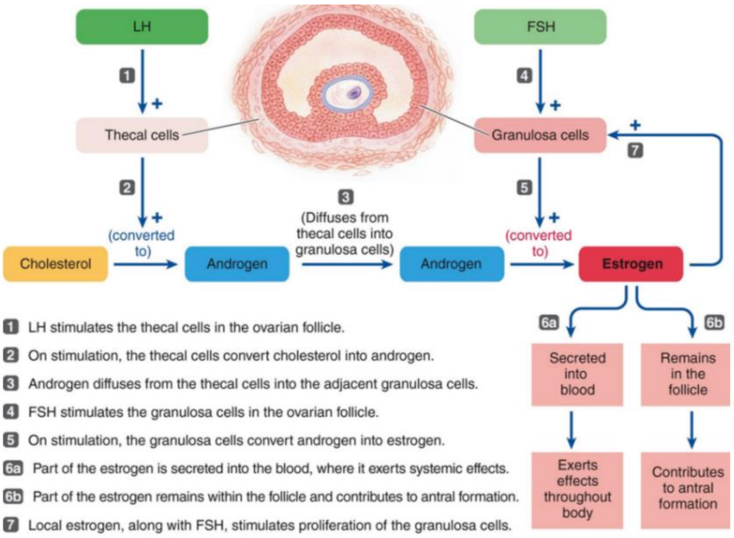
- Multiple primary follicles (a primary oocyte surrounded by a single layer of granulosa cells) are stimulated to develop
    - A zona pellucida develops to surround the primary oocyte
- The granulosa cells develop and differentiate to form both granulosa and thecal cells (known collectively as follicular cells). This results in a thicker layer of follicular cells around a primary oocyte.
    - As the follicles grow, they begin releasing oestrogen
    - The granulosa cells also secrete a thick oestrogen-rich fluid that begins to form an antrum within the follicle
    - Prior to antrum formation, the primary follicle is also known as a pre-antral follicle
- The granulosa and theca cells continue to develop and an antrum forms within the layer of granulosa cells, forming a secondary or antral follicle containing a primary oocyte
    - If more than one follicle develops to this stage, two or more eggs can be ovulated resulting in the possibility of fraternal twins or triplets etc.
- The antrum continues to grow until one secondary follicle becomes dominant, containing a large antrum. The primary oocyte becomes a secondary oocyte as it undergoes the final stages of meiosis I, turning the follicle into a mature or Graafian follicle.
    - The enlargement of the secondary/antral follicle causes a bulging on the surface of the ovary
- The oocyte is ovulated as it bursts through the wall of the ovary.
    - This occurs around day 14 of the cycle
    - A small amount of granulosa cells remains around the ovulated secondary oocyte, forming the corona radiata.
    - The rest of the follicle, including the large antrum, remain within the ovary.

The luteal phase:

- The follicular remnants form the corpus luteum
    - The CL is responsible for large amounts of progesterone production
    - The CL undergoes morphological changes wherein it becomes yellow and fatty due to it's hormone-producing function
- If pregnancy does not occur, the CL degenerates, moving through the stages of degeneration, forming the corpus albicans (a small white structure). If pregnancy occurs, the influence of beta-HCG will prolong the life of the CL, allowing it to continue producing progesterone to support the pregnancy until the placenta develops and takes over this role.

Control of the ovarian cycle involves both hypothalamic and pituitary hormones, under the influence of sex hormones secreted by the follicles and CL themselves.

- GnRH is released from the hypothalamus in a pulsatile fashion
    - The pulsatility of the release can favour either FSH or LH production
        - Increased frequency pulses preferentially cause LH secretion
        - Decreased frequency pulses preferentially cause FSH secretion
- GnRH causes the release of LH and FSH from the pituitary gland
- LH and FSH cause the development of the follicle
    - The follicle begins to secrete oestrogen and inhibin
        - Oestrogen has an indirect negative feedback effect on the hypothalamus via kiss1 neurons early in the follicular stage
        - Inhibin has a direct negative feedback onto the FSH-secreting cells of the pituitary gland



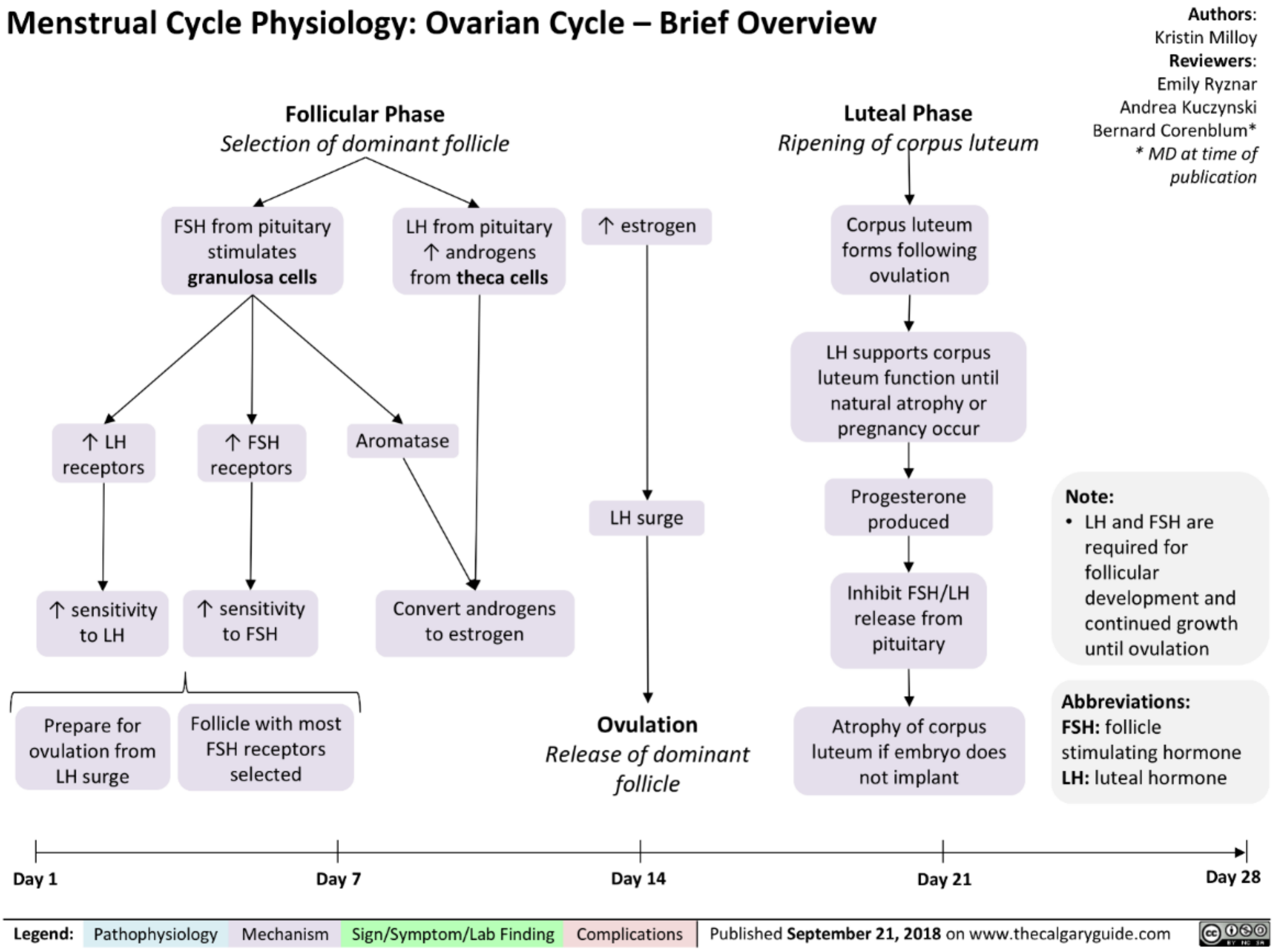
1 LH stimulates the thecal cells in the ovarian follicle.
2 On stimulation, the thecal cells convert cholesterol into androgen.
3 Androgen diffuses from the thecal cells into the adjacent granulosa cells.
4 FSH stimulates the granulosa cells in the ovarian follicle.
5 On stimulation, the granulosa cells convert androgen into estrogen.
6a Part of the estrogen is secreted into the blood, where it exerts systemic effects.
6b Part of the estrogen remains within the follicle and contributes to antral formation.
7 Local estrogen, along with FSH, stimulates proliferation of the granulosa cells.

- Although oestrogen has a negative feedback effect on FSH and LH release in the early follicular phase, in the late follicular phase oestrogen actually has a positive feedback impact that causes the LH surge. At this stage, oestrogen levels are at their highest due to the increased size of the follicle.
    - The reason FSH does not surge is likely because inhibin selectively prevents FSH secretion
- The LH surge causes ovulation of the mature follicle containing the secondary oocyte
- The remaining CL secretes high levels of progesterone and low levels of oestrogen
    - Progesterone from the CL has an indirect negative feedback effect on GnRH secretion via Kiss1 neurons as well as a direct negative feedback effect on FSH an LH release at the pituitary
    - Oestrogen from the CL has it's normal indirect negative feedback effect on the hypothalamus via Kiss1 neurons in the luteal phase
- Under the influence of negative feedback, FSH and LH levels drop
- If there is no pregnancy, the degeneration of the CL withdraws the negative feedback effects and in the late luteal phase FSH levels begin to rise again

    - FSH levels are preferentially increased in the late luteal phase due to the low frequency GnRH pulses
    - This allows for the beginning of development of new primary oocytes during
- Newly developing follicles begin to secrete oestrogens and the cycle begins again

Energy metabolism can impact the hormonal control of the ovarian cycle. For example, poor nutrition can lead to anovulation and increased obesity and leptin can cause increased oestrogen levels which can increase negative feedback systems, which can result in decreased ovulation and thus decreased fertility.

THE UTERINE CYCLE



Menstrual Cycle Physiology: Ovarian Cycle – Brief Overview

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Follicular Phase
Selection of dominant follicle

FSH from pituitary stimulates **granulosa cells**

LH from pituitary ↑ androgens from **theca cells**

↑ LH receptors

↑ FSH receptors

Aromatase

↑ sensitivity to LH

↑ sensitivity to FSH

Convert androgens to estrogen

Prepare for ovulation from LH surge

Follicle with most FSH receptors selected

↑ estrogen

LH surge

Ovulation
Release of dominant follicle

Luteal Phase
Ripening of corpus luteum

Corpus luteum forms following ovulation

LH supports corpus luteum function until natural atrophy or pregnancy occur

Progesterone produced

Inhibit FSH/LH release from pituitary

Atrophy of corpus luteum if embryo does not implant

Note:
- LH and FSH are required for follicular development and continued growth until ovulation

Abbreviations:
FSH: follicle stimulating hormone
LH: luteal hormone

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications | Published **September 21, 2018** on www.thecalgaryguide.com

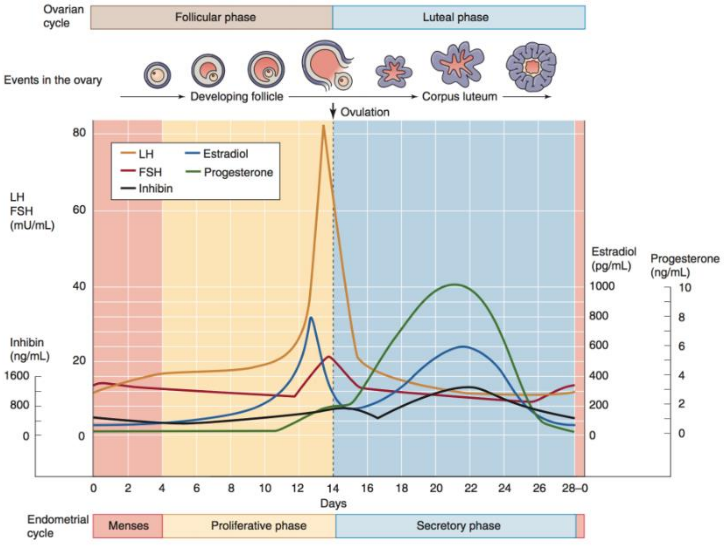
The uterine cycle is composed of three stages, the menstrual phase, the proliferative phase and the secretory phase, which generally coincide with the phases of the ovarian cycle. This is because the two processes are intimately linked functionally but also because they are controlled by the same hormonal mechanisms.

The menstrual phase:

- The menstrual phase is the phase during which bleeding occurs and is considered to the be the start of the cycle
    - Shedding occurs because of the withdrawal of progesterone and oestrogen which supported the upper layers of the endometrium in the uterus (the functionalis layer)
    - Mechanisms underlying shedding of the functionalis include prostaglandin production inducing hypoxia of spiral arteries and MMP upregulation.

The proliferative phase:

- The proliferative phase involves the production of a new stratum functionalis layer in the endometrium after shedding of the old layer during menstruation as well as a thinning of the cervical mucus to allow for easy sperm entry
    - The stratum functionalis is grown on top of the existing stratum basalis that is not shed
    - The stratum basalis has straight arteries while the stratum functionalis only has spiral arteries
- The proliferative stage is influenced largely by oestrogen secreted from the developing follicle
- The stratum functionalis grows from around 2mm to 10mm thickness in the 10-14 days that the stage lasts.
- The growth involves:



Menstrual Cycle Physiology: the Uterine Cycle

Author: Yan Yu*
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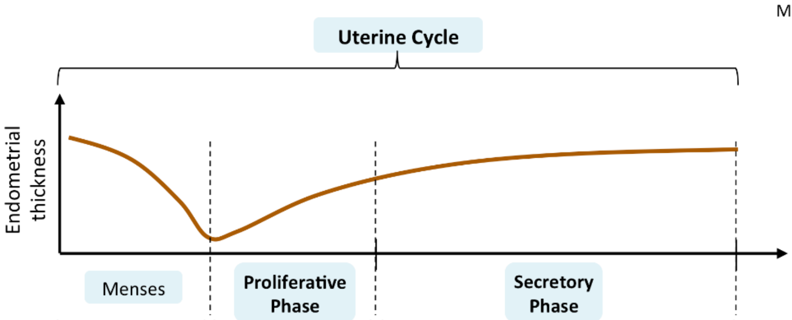
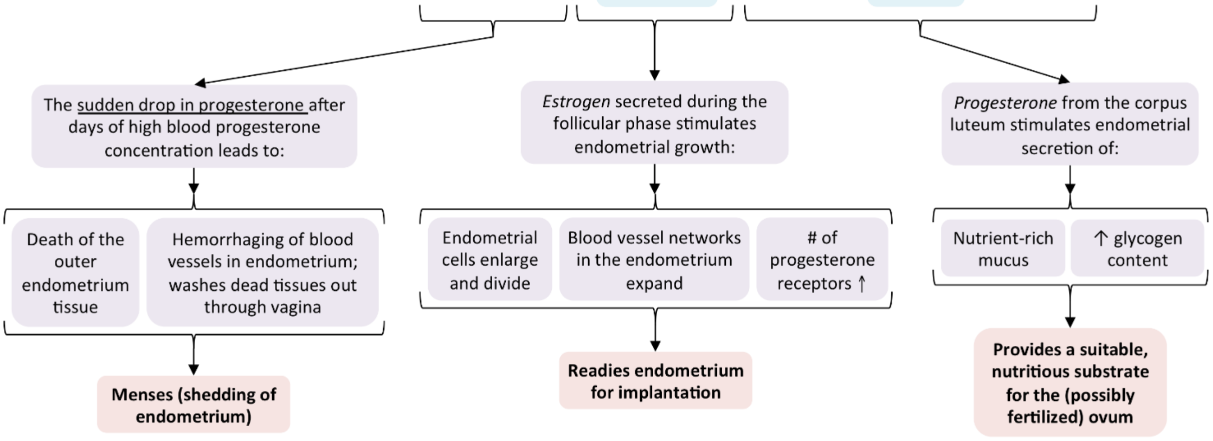
The endometrium has receptors for ovarian hormones! Changes in structure and secretory capacity of the endometrium occur in response to hormonal changes in the ovarian cycle.





The sudden drop in progesterone after days of high blood progesterone concentration leads to:

- Death of the outer endometrium tissue
- Hemorrhaging of blood vessels in endometrium; washes dead tissues out through vagina

Menses (shedding of endometrium)

Estrogen secreted during the follicular phase stimulates endometrial growth:

- Endometrial cells enlarge and divide
- Blood vessel networks in the endometrium expand
- # of progesterone receptors ↑

Readies endometrium for implantation

Progesterone from the corpus luteum stimulates endometrial secretion of:

- Nutrient-rich mucus
- ↑ glycogen content

Provides a suitable, nutritious substrate for the (possibly fertilized) ovum

Note: The drop in progesterone concentration that triggers menses is the physiologic basis of the **progesterone withdrawal challenge** (used to test if a woman is hypo-estrogenized). If a woman is making estrogen (i.e. if ovaries/follicles are functioning), endometrium will be built up, so a short course of progesterone (10-14 days) will induce menses within 3 days once the progesterone is stopped. If woman is hypo-estrogenized (i.e. ovarian failure, menopause) → no endometrium → no menses upon termination of progesterone.

Menstrual Cycle Physiology: The Hypothalamic-Pituitary-Ovarian Axis

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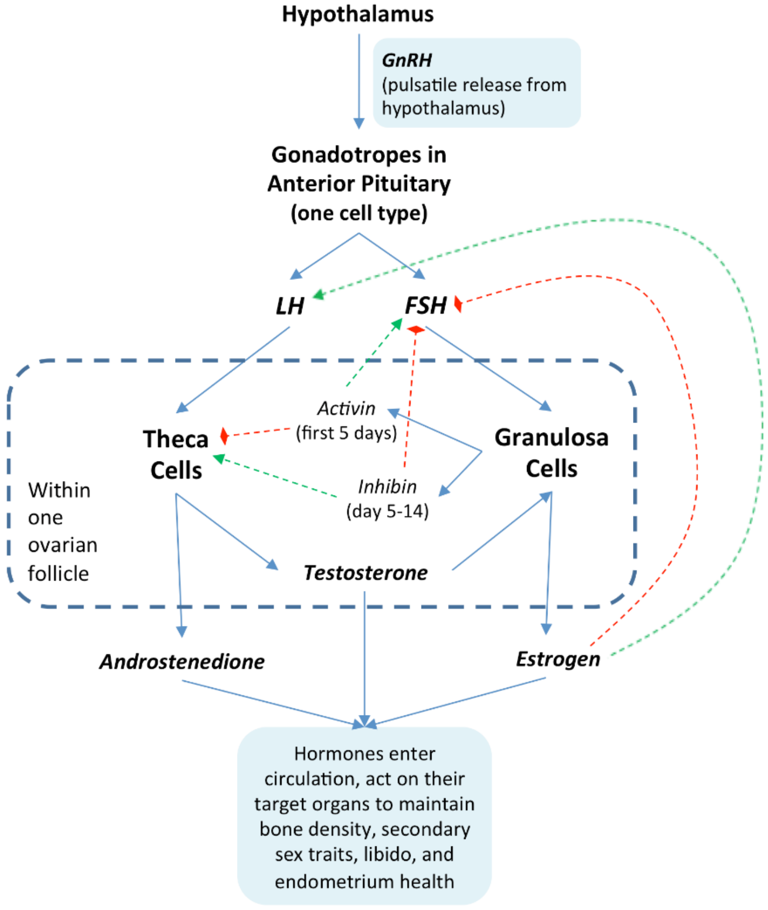


Hormones enter circulation, act on their target organs to maintain bone density, secondary sex traits, libido, and endometrium health

Abbreviations and Legend:

- **GnRH**: Gonadotropin Releasing Hormone
- **FSH**: Follicle Stimulating Hormone
- **LH**: Luteinizing Hormone

- - - -▶ Activation, or Positive Feedback
- - - -♦ Inhibition, or Negative Feedback

Estrogen, when released:

- *Negatively* feeds back on the hypothalamus and anterior pituitary to ↓ FSH production
- Positively feeds back on the hypothalamus and anterior pituitary to ↑ LH production

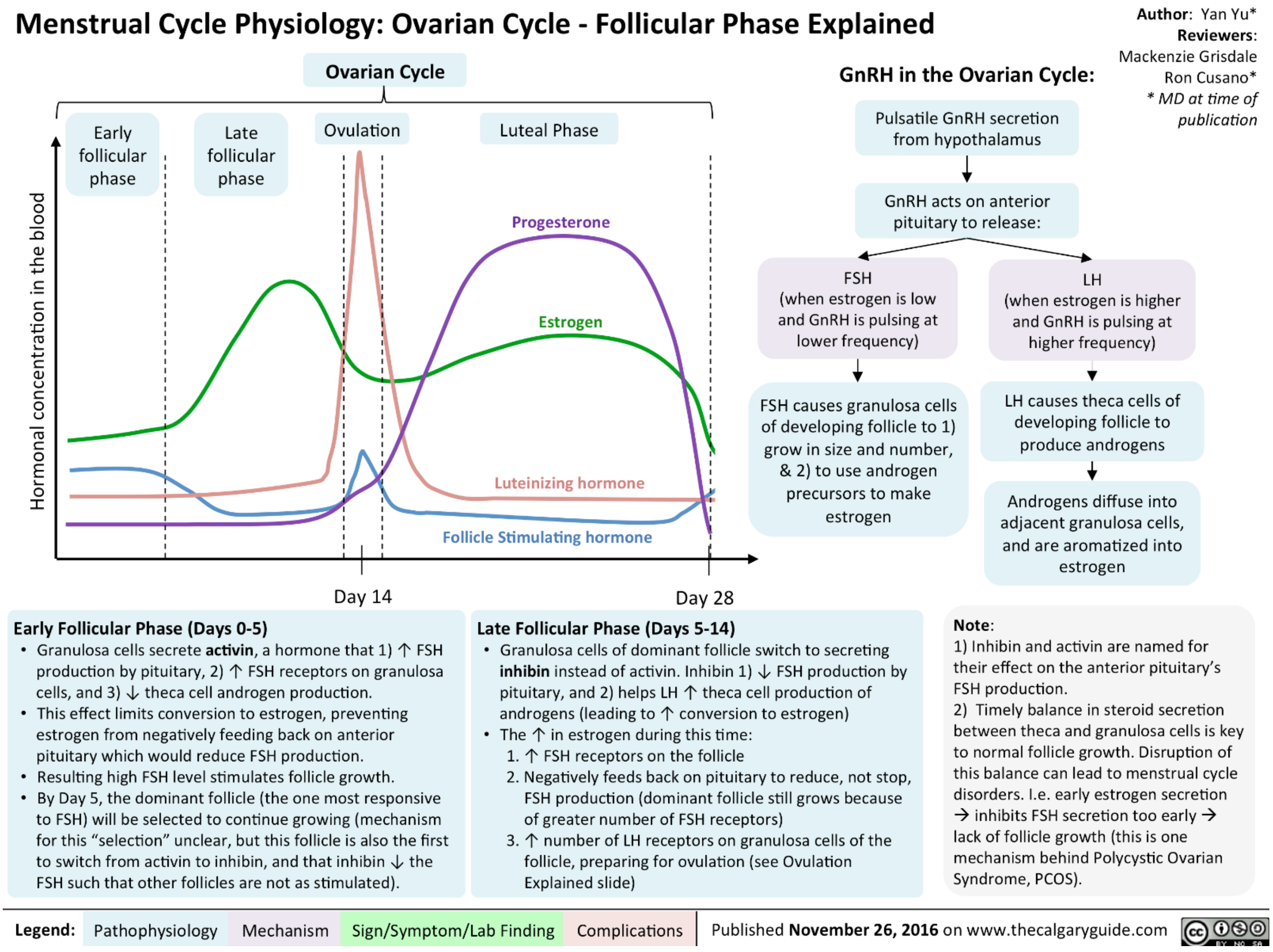
Note: the hormones of the menstrual cycle vary in terms of when and how much they are secreted, according to the various phases of the cycle. This flow-chart is simply meant to capture the main players and their functions in the menstrual cycle, in as much detail as a medical student needs to know.
For more detailed explanations, please consult the other Menstrual Cycle Physiology slides.

○ Increases in vasculature (spiral vessels) that extend into the lamina propria

  - Epithelial cell proliferation
  - Lengthening and packing of glands with increases in gland receptors for oestrogen and progesterone

Secretory phase:

- This phase begins after ovulation and lasts until menses begins
- The endometrium thickens and glands begin accumulating glycogen in preparation for implantation of the fertilised zygote (also known as pre-decidualisation)
- This occurs under the influence of progesterone
  - Progesterone inhibits further proliferation and antagonises the effects of oestrogen
- During this stage progesterone also induces thickening of the cervical mucus to prevent further sperm entering



Menstrual Cycle Physiology: Ovarian Cycle - Follicular Phase Explained

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** MD at time of publication*

GnRH in the Ovarian Cycle:

Pulsatile GnRH secretion from hypothalamus

GnRH acts on anterior pituitary to release:

FSH (when estrogen is low and GnRH is pulsing at lower frequency)

FSH causes granulosa cells of developing follicle to 1) grow in size and number, & 2) to use androgen precursors to make estrogen

LH (when estrogen is higher and GnRH is pulsing at higher frequency)

LH causes theca cells of developing follicle to produce androgens

Androgens diffuse into adjacent granulosa cells, and are aromatized into estrogen

Early Follicular Phase (Days 0-5)

- Granulosa cells secrete **activin**, a hormone that 1) ↑ FSH production by pituitary, 2) ↑ FSH receptors on granulosa cells, and 3) ↓ theca cell androgen production.
- This effect limits conversion to estrogen, preventing estrogen from negatively feeding back on anterior pituitary which would reduce FSH production.
- Resulting high FSH level stimulates follicle growth.
- By Day 5, the dominant follicle (the one most responsive to FSH) will be selected to continue growing (mechanism for this "selection" unclear, but this follicle is also the first to switch from activin to inhibin, and that inhibin ↓ the FSH such that other follicles are not as stimulated).

Late Follicular Phase (Days 5-14)

- Granulosa cells of dominant follicle switch to secreting **inhibin** instead of activin. Inhibin 1) ↓ FSH production by pituitary, and 2) helps LH ↑ theca cell production of androgens (leading to ↑ conversion to estrogen)
- The ↑ in estrogen during this time:
  1. ↑ FSH receptors on the follicle
  2. Negatively feeds back on pituitary to reduce, not stop, FSH production (dominant follicle still grows because of greater number of FSH receptors)
  3. ↑ number of LH receptors on granulosa cells of the follicle, preparing for ovulation (see Ovulation Explained slide)

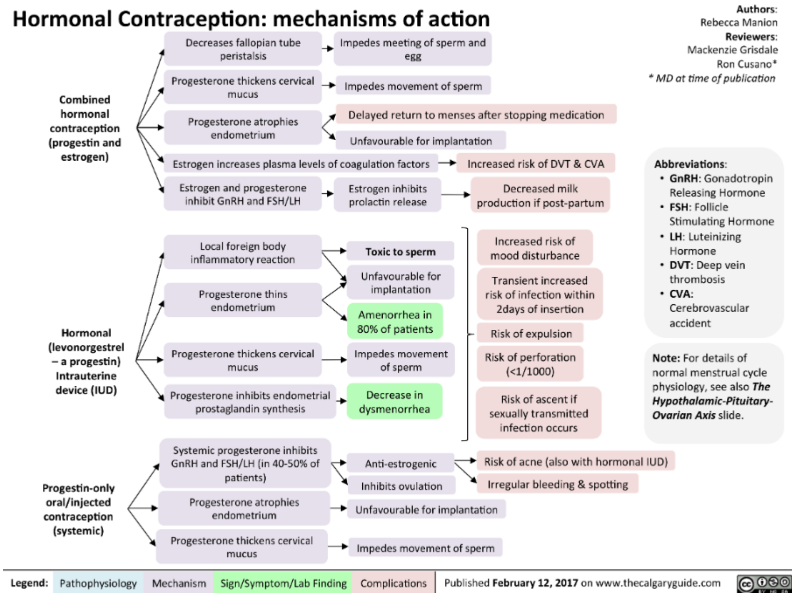
Note:
1) Inhibin and activin are named for their effect on the anterior pituitary's FSH production.
2) Timely balance in steroid secretion between theca and granulosa cells is key to normal follicle growth. Disruption of this balance can lead to menstrual cycle disorders. I.e. early estrogen secretion → inhibits FSH secretion too early → lack of follicle growth (this is one mechanism behind Polycystic Ovarian Syndrome, PCOS).

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications | Published **November 26, 2016** on www.thecalgaryguide.com

HORMONAL CONTRACEPTIVE

Hormonal contraceptives work via eliciting a negative feedback effect on the pituitary and the hypothalamus release of FSH and LH. This is because they contain either oestrogen and/or progesterone.

- The OCP is the most used form of hormonal contraceptive: estrogen and progesterone are taken daily to suppress ovulation, induce endometrial changes and thicken cervical mucus to prevent sperm entering
- Progesterone only contraceptives can be used in certain circumstances and are common with breastfeeding women. These are available in pill form as well as in the form of injections and Mirena. Progesterone only pills do not always totally block ovulation.
- Male contraceptives work in the same way (by eliciting negative feedback) but have had safety and efficacy issues thus far.



Hormonal Contraception: mechanisms of action

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Combined hormonal contraception (progestin and estrogen)
Decreases fallopian tube peristalsis → Impedes meeting of sperm and egg
Progesterone thickens cervical mucus → Impedes movement of sperm
Progesterone atrophies endometrium → Delayed return to menses after stopping medication; Unfavourable for implantation
Estrogen increases plasma levels of coagulation factors → Increased risk of DVT & CVA
Estrogen and progesterone inhibit GnRH and FSH/LH → Estrogen inhibits prolactin release → Decreased milk production if post-partum

Hormonal (levonorgestrel – a progestin) Intrauterine device (IUD)
Local foreign body inflammatory reaction → **Toxic to sperm**; Unfavourable for implantation
Progesterone thins endometrium → Unfavourable for implantation; Amenorrhea in 80% of patients
Progesterone thickens cervical mucus → Impedes movement of sperm
Progesterone inhibits endometrial prostaglandin synthesis → Decrease in dysmenorrhea
Increased risk of mood disturbance
Transient increased risk of infection within 2days of insertion
Risk of expulsion
Risk of perforation (<1/1000)
Risk of ascent if sexually transmitted infection occurs

Progestin-only oral/injected contraception (systemic)
Systemic progesterone inhibits GnRH and FSH/LH (in 40-50% of patients) → Anti-estrogenic → Risk of acne (also with hormonal IUD); Irregular bleeding & spotting
Systemic progesterone inhibits GnRH and FSH/LH (in 40-50% of patients) → Inhibits ovulation
Progesterone atrophies endometrium → Unfavourable for implantation
Progesterone thickens cervical mucus → Impedes movement of sperm

Abbreviations:
- **GnRH**: Gonadotropin Releasing Hormone
- **FSH**: Follicle Stimulating Hormone
- **LH**: Luteinizing Hormone
- **DVT**: Deep vein thrombosis
- **CVA**: Cerebrovascular accident

Note: For details of normal menstrual cycle physiology, see also ***The Hypothalamic-Pituitary-Ovarian Axis*** slide.

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications | Published **February 12, 2017** on www.thecalgaryguide.com

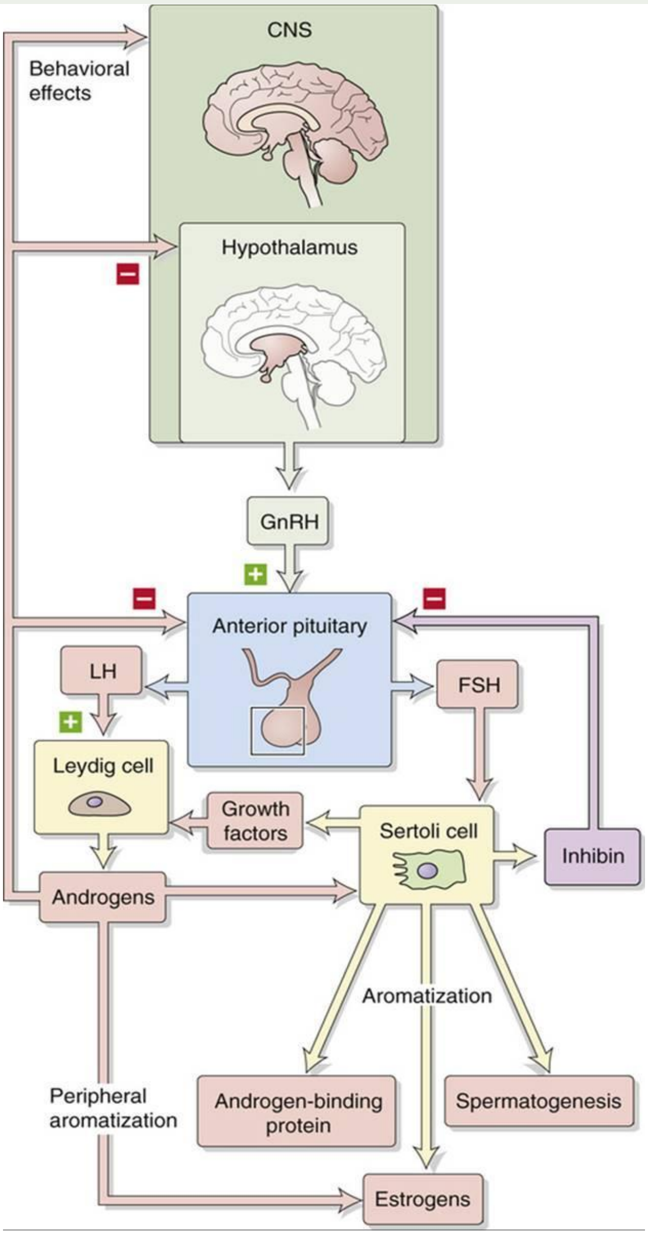
MALE REPRODUCTIVE PHYSIOLOGY

The testes are the component of the male reproductive system responsible for the production of sperm. These are located outside the body in the scrotum, which extends from anterior abdominal wall and is kept at a regulated temperature by the action of the dartos and cremaster muscle as well as by heat exchange that occurs between the artery and vein system. This is essential because of the need for spermatogenesis to occur in a certain temperature range. As the sperm are produced, they are moved through the seminiferous tubules to the straight tubules and then to the rete testes. From here they move to the efferent ductules and into the epididymis. This process is important because during this passage they continue to develop and mature. From the epididymis they move into the ductus deferens. This tube connects to the seminal vesicles on the posterior aspect of the prostate to form the ejaculatory ducts, which move into the prostatic urethra. The sperm is now mixed with seminal fluid and is ejaculated through the penis.

This process is controlled by GnRH that is released in a pulsatile manner from the hypothalamus. Just as in the female, this leads to the production of FSH and LH, which affect the testes of the male. This causes the production of further hormones that act to promote spermatogenesis as well as having peripheral effects. The hormones also cause a negative feedback process onto the hypothalamus.

- Inhibin produced by Sertoli cells acts on the anterior pituitary to downregulate FSH secretion
- Testosterone produced by the Leydig cells has a direct effect on the release of sex hormones from the anterior pituitary as well as acting via an indirect negative feedback system via Kiss1 neurons in the brain, causing a downregulation of GnRH production

SPERMATOGENESIS:



The process of spermatogenesis takes around 70 days. Around 50 days of this are spent in the testes themselves, while the rest is spent in the epididymis for further development.

- Primordial germ cells of the male migrate to the gonad during embryogenesis, becoming spermatogonium
- Spermatogonium undergo mitosis to form spermatogonia
  - Spermatogonia have a normal diploid 2N chromosomal make up
- Beginning at puberty, spermatogonia are recruited to develop further, and this process continue throughout life
- Spermatogonia undergo meiosis I to form primary spermatocytes
  - Primary spermatocytes contain 4N DNA
- After prophase I, the primary spermatocytes become secondary spermatocytes
  - Secondary spermatocytes contain haploid duplicated chromosomes, meaning they have 2N DNA
- Secondary spermatocytes enter into meiosis II and become spermatids
  - Spermatids have a shape that much more closely resembles the common conception of sperm
  - Spermatids have a haploid 1N DNA
  - They are still not fully mature and are essentially immobile
    - The cells until this point maintain cytoplasmic ridges between one another; total physical separation of the cells does not occur until spermiogenesis
- Spermatids transform into spermatozoa via the process of spermiogenesis
  - This involves a reduction in cytoplasmic content, increase in mitochondrial content, formation of the acrosome, condensation of the nucleus and growth of the tail
  - The spermatozoa are still immobile at the completion of spermiogenesis
- The spermatozoa move into the epididymis via the tubular pathway and here they are able to gain forward motility, their ability to fertilise is increased, their acrosome is matured and they gain the ability to recognise and bind to the zona pellucida of the ovum.
- Capacitation is the final step of spermatozoan development, and it occurs in the female reproductive tract just prior to fertilisation.
  - This involves the acrosome reaction, allowing fusion with the plasma membrane of the oocyte, as well as hyperactivated tail movements.

Spermatogenesis occurs within the seminiferous tubules. The most immature spermatogonium are located deep within the tubule epithelium while the spermatids are located at the apical surface. This process is promoted by the actions of Sertoli cells.

- Sertoli cell at the basement membrane of the cell have extremely tight junctions between them; this is important for the formation of the blood-testes barrier. This is important because of the chromosomal abnormality of the sperm, they would likely otherwise be attacked and destroyed by circulating immune cells.
- The blood-testes barrier is also key to maintaining a microenvironment for the hormones produced by the cells of the testes.

The two key cells of the testes are the Leydig cell and the Sertoli cell, and both are important for spermatogenesis. They work closely together to promote testosterone production and spermatogenesis.

- The Sertoli cell (also known as the nurse cell) are located within the seminiferous tubules and are intimately linked to the development of the spermatozoa
  - Sertoli cells are responsive to male FSH

    - Sertoli cells produce numerous growth factors and other substances that directly influence the development of the spermatozoa
    - Sertoli cells are also very responsive to Leydig-cell produced testosterone
    - Sertoli cells produce inhibin to downregulate FSH production
    - Sertoli cells also contain aromatase enzyme, allowing them to convert Leydig testosterone into estradiol and other growth factors
- The Leydig cells are located in the interstitium of the testes
    - Leydig cells are responsive to LH
    - Leydig cells produce androgens, particularly testosterone in response to LH stimulation, which can then act on Sertoli cells
        - The majority of this testosterone acts locally, but it can also have systemic effects
    - Leydig cells are responsive also to growth factors and substances produced by the Sertoli cells

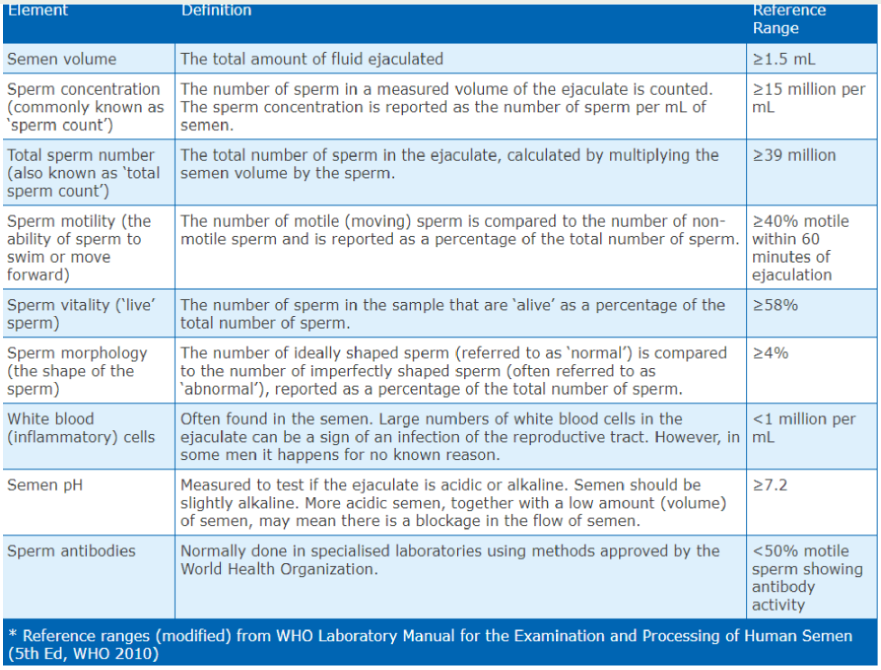
Inhibition of GnRH production at the hypothalamus in males is controlled via kiss1 neurons in the CNS. This is because the hypothalamus does not have direct receptors for testosterone. This causes the release of kisspeptin into the hypothalamus, which downregulates release. This also occurs with oestrogen and progesterone in females too.

SEMEN COMPOSITION:

When the sperm are ejaculated, they are combined with a nutrient-rich fluid that helps support fertilisation. The final semen contains only around 10% sperm. These substances are produced by the seminal vesicles, the prostate etc and are mixed with the sperm as they move through the reproductive tract. The key components include:

- Fructose: important for protecting and activating sperm as well as providing energy
- Hormones
- Alkaline fluid: neutralizes the acid of the urethra and the vagina
- Prostaglandins: decrease the viscosity of the cervical mucus, stimulate reverse peristalsis in the uterus
- Clotting factors: causes seminal coagulation after ejaculation
- Fibrinolysin: causes the breakdown of the semen clot
- miRNA capable of exerting effects on the female reproductive tract

In addition to supporting the life of the sperm, the semen is likely to interact with the tissues of the female reproductive tract. For example, prostaglandins upregulate an immune response which may be important for the defence against STIs. This is an ongoing area of research.



Element	Definition	Reference Range
Semen volume	The total amount of fluid ejaculated	≥1.5 mL
Sperm concentration (commonly known as 'sperm count')	The number of sperm in a measured volume of the ejaculate is counted. The sperm concentration is reported as the number of sperm per mL of semen.	≥15 million per mL
Total sperm number (also known as 'total sperm count')	The total number of sperm in the ejaculate, calculated by multiplying the semen volume by the sperm.	≥39 million
Sperm motility (the ability of sperm to swim or move forward)	The number of motile (moving) sperm is compared to the number of non-motile sperm and is reported as a percentage of the total number of sperm.	≥40% motile within 60 minutes of ejaculation
Sperm vitality ('live' sperm)	The number of sperm in the sample that are 'alive' as a percentage of the total number of sperm.	≥58%
Sperm morphology (the shape of the sperm)	The number of ideally shaped sperm (referred to as 'normal') is compared to the number of imperfectly shaped sperm (often referred to as 'abnormal'), reported as a percentage of the total number of sperm.	≥4%
White blood (inflammatory) cells	Often found in the semen. Large numbers of white blood cells in the ejaculate can be a sign of an infection of the reproductive tract. However, in some men it happens for no known reason.	<1 million per mL
Semen pH	Measured to test if the ejaculate is acidic or alkaline. Semen should be slightly alkaline. More acidic semen, together with a low amount (volume) of semen, may mean there is a blockage in the flow of semen.	≥7.2
Sperm antibodies	Normally done in specialised laboratories using methods approved by the World Health Organization.	<50% motile sperm showing antibody activity

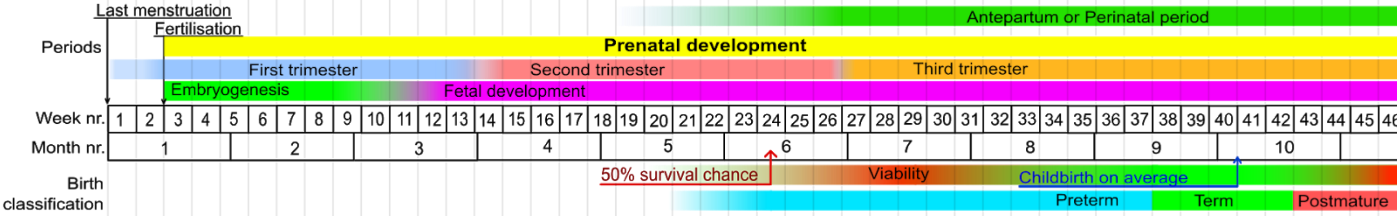
* Reference ranges (modified) from WHO Laboratory Manual for the Examination and Processing of Human Semen (5th Ed, WHO 2010)

Semen analysis is important for investigations into fertility. This looks at many parameters, such as volume, concentration, vitality and pH.

Some pathologies affecting sperm include:

- Oligozoospermia: decreased number of sperm
- Azoospermia: complete absence of sperm
- Abnormal sperm motility
- Abnormal sperm morphology
- Aspermia: absence of ejaculate fluid

EMBRYOLOGY AND PREGNANCY



Week	Day	Carnegie Stage	Features
1	1	1	**Fertilisation**
1	2	1	Cleavage continues occurring causing cell size to decrease
1	3	2	**Formation of morula**
1	4	3	**Blastocyst formed** **Loss of zona pellucida**
1	6	4	Beginning of **implantation** Formation of amniotic cavity
2	7-12	5	Blastocyst fully implanted **Bilaminar disc formed**
2	13	6	**Primitive streak forms** Intervillous spaces have formed and filled with blood

			Extraembryonic coelom formation begins
3	16	7	**Gastrulation** commences **Notochord** forms
3	18	8	Neural plate and neural groove form
3	20	9	**Heart begins to form** Vasculature begins to form **Somites form**
4	22	10	Cranial flexion occurs **Heart begins to pump** Liver begins to form Pharyngeal arches begin to form
4	24	11	**Primordial germ cells migrate** Cranial neuropore closes Optic pits begin to form
4	26	12	**Upper limb buds form** Pancreatic bud forms
4	28	13	Spleen forms **Lower limb buds form**
5	32	14	Spinal nerves begin sprouting **Metanephros begins to develop** Stomach curves and **intestinal loops begin to form** Cerebral hemispheres are visible
5	33	15	**Hand plates develop** **Medial and lateral nasal processes form** Cranial nerve ganglia begin to form
6	37	16	Gut tube lumen is occluded Ear begins to form **Kidneys begin to ascend** **Foot plates develop** Genital ridges form
6	41	17	Dental laminae form Melanocytes enter dermis
7	44	18	**Skeletal ossification begins** Sertoli cells differentiate (male) Nipples and first hair follicles develop
7	47	19	Trunk elongates and straightens
8	50	20	Intestinal loops complete counter clockwise rotation **Mullerian ducts degenerate (male)** Upper limbs bend
8	52	21	**Hands and feet rotate to midline**
8	54	22	Eyelids developed
8	56	23	Chorionic cavity is obliterated Lumen of gut is almost complete recanalized

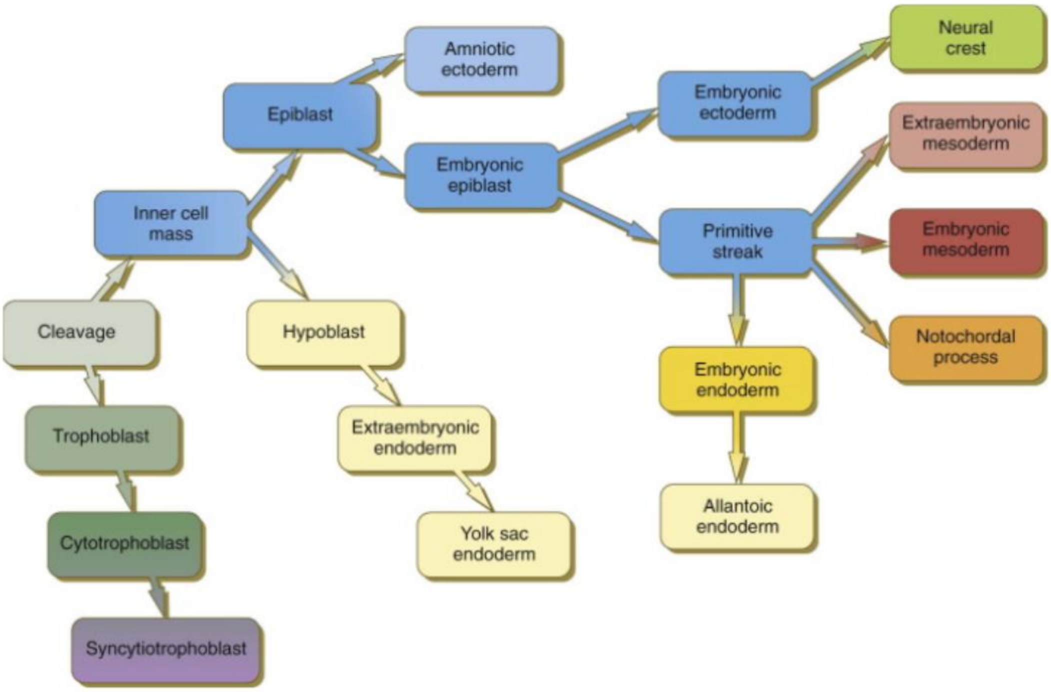
Foetal Stage Begins

Month	Features
4	**Eyes migrated to front of face** Seminal vesicle forms Bone marrow haematopoiesis begins Ovaries contain primordial follicles
5	**Testes begin descent** **TSH released by foetus**
6	**Surfactant begins to be secreted** Odour detection and taste are functional
7	Eyelids begin to open **Testes descend into scrotum** Splenic erythropoiesis stops Sulci and gyri appear on brain
8	Skin is fully developed and is smooth and soft **Testes finish descent**
9	**Larger amounts of pulmonary surfactant are produced** Ovaries still above pelvic brim Umbilical cord attachment becomes centralised in abdomen

By the end of the first trimester all major body systems are developed:
- Sex is distinguishable
- Neck is well defined
- Upper limbs are well developed
- Intestines have returned to the abdomen after herniation

By the end of the second trimester:
- Head and body hair are distinguishable
- Movements are quickening
- Most major anomalies can be detected via ultrasound

By the end of the third trimester:
- CNS has matured
- Testes are in scrotum



Determinants of foetal growth include:
- Insulin-like growth factor
- Insulin and glucose
    - Maternal glucose crosses easily into the placenta but insulin cannot
    - The foetus produces insulin in response to maternal glucose
- Glucocorticoids
- Thyroid hormones
- Epidermal growth factor

FERTILISATION

Fertilisation occurs when the haploid ovum is fertilised, usually in the ampulla of the uterine tube. This forms a diploid zygote.

Fertilisation occurs when a capacitated spermatocyte binds to the zona pellucida of the ova.
- Calcium levels within the cell rise and form acrosomal exocytosis releasing the hydrolytic enzymes
    - This is known as the acrosomal reaction
- The hydrolytic enzymes dissolve the zona pellucida
- The tail motion of the spermatocyte pushes the head towards the membrane of the oocyte
- The membranes of the spermatocyte and the oocyte fuse
- The contents of the spermatocyte head enter the cell
    - Usually the tail of the sperm remains on the outside
- This fusion causes an increase in intracellular calcium within the oocyte
- The calcium within the cell causes exocytosis of enzyme-containing granules from the oocyte
    - This is known as the cortical reaction
    - These enzymes cause the hardening of the zona pellucida ZP3 proteins
    - This prevents polyspermy
- The calcium within the cell also induces the oocyte's completion of meiosis II to form the female pronuclei
    - The second polar body is formed
- The male and female pronuclei merge to form the zygote
    - This occurs due to the formation of a mitotic spindle between them

The zygote then undergoes cleavage into two blastomeres – this process of cleavage continues for up to three days. Each cleavage doubles the number of cells. At this point, the ball of cells is still surrounded by zona pellucida so the cells get smaller with each division.

The ball of cells is called a morula when it reaches 16 cells.

The morula is moved into the uterine cavity for implantation. During this time, the cells undergo further divisions and begin producing a fluid substance which forms a cavity within the cells. This is known as the blastocyst. This occurs approximately around day 4.
- The blastocyst is composed of an inner cell mass or embryoblast and an outer cell mass or trophectoderm
    - This is the first cellular specialisation that will occur

IMPLANTATION

Proteases from the secretory endometrium cause the breakdown of the zona pellucida surrounding the blastocyst. This process is known as hatching.
- This allows for the blastocyst products to directly influence the endometrium and promote receptivity
- It also allows for endometrial products to influence the embryo (i.e. nutrients etc)

The embryoblast or inner cell mass differentiates into a hypoblast and epiblast.

The amniotic cavity forms (initially small) between the epiblast and trophoblast as fluid collects between these two layers.

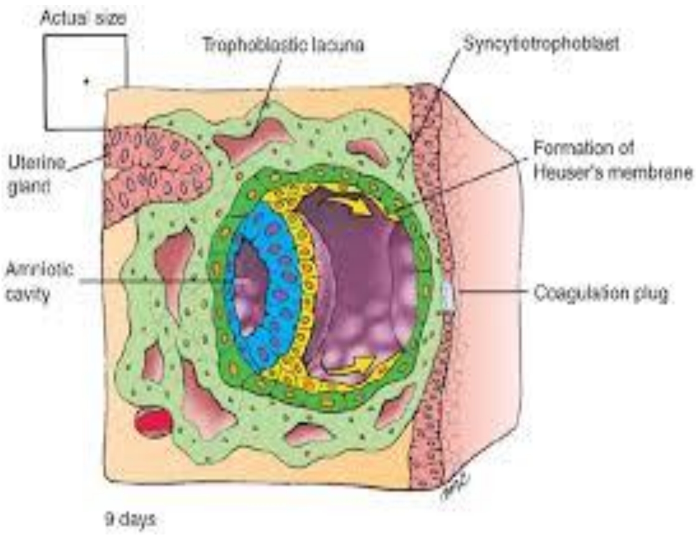
- The amniotic cavity becomes surrounded by epiblast cells
    - By week 8 of gestation, the amnion will surround the entire embryo
- At this point, the cells are known as the bilaminar germ disc

At this stage of development, the endometrium undergoes decidualisation to increase receptivity. The stratum basalis and stratum functionalis are now called the decidua functionalis and decidua basalis.

The blastocyst implants into the receptive endometrium between 6-7 days after fertilisation. This occurs due to binding of receptors (integrins, selectins etc) on the endometrium and outer cell mass and under the influence of oestrogen and progesterone – the corpus luteum is essential for promoting the receptivity of the uterus. The binding of these receptors causes the release of chemokines which allow for stabilisation and implantation.

The blastocyst will always implant into the endometrium on the side of inner cell mass growth. Implantation occurs in three stages:

- Apposition: the blastocyst is apposed to the uterine wall
- Adhesion: the blastocyst increases contact with endometrial cells
- Invasion: the blastocyst penetrates the endothelium\



The hypoblast sends out endodermal cells into the blastocyst cavity and forms the primary yolk sac. The second wave of endodermal cells transforms the primary yolk sac into the secondary yolk sac. The extraembryonic mesoderm forms and fills the remaining blastocyst cavity with cells. After splitting of the extraembryonic mesoderm, the definitive yolk sac is formed.

- The yolk sac is the site of early embryonal haematopoiesis
- The yolk sac is the site of origin of primordial germ cells

GASTRULATION

Gastrulation is the formation of the trilaminar germ disc from the bilaminar germ disc. At around day 15, a groove forms in the midsagittal plane of the developing embryo which is known as the primitive streak. As it gets deeper it is called the primitive groove. The cranial end of the groove becomes deeper and is known as the primitive node.

- The primitive pit end of the embryo will develop into the cranial end of the foetus

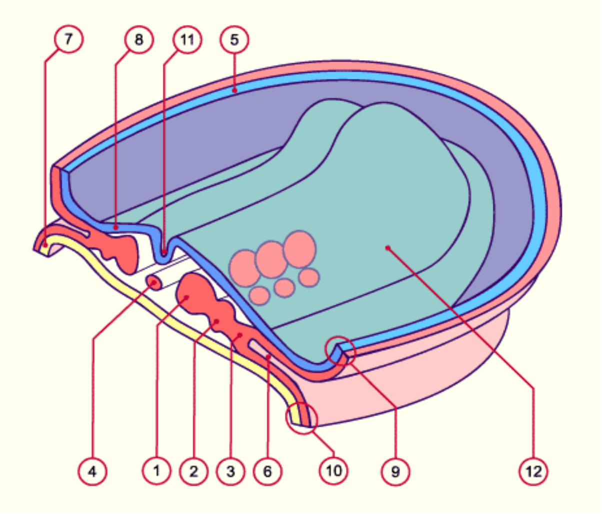
Epiblast cells move towards the primitive streak, enter the streak and migrate underneath the epiblast.

- The hypoblast layer is replaced by endodermal cells
- The intraembryonic mesoderm forms in the middle
- The top layer becomes the endoderm

The mesoderm quickly arranges itself to form three separate mesodermal structures:

- The paraxial mesoderm (lateral to the notochord)
    - Will form the axial skeleton, the dermis and voluntary musculature
    - Will form somites
- The intermediate mesoderm
    - Will form the genital and urinary systems
- The lateral plate mesoderm (splanchnic and somatic; separated by the intraembryonic coelom)
    - The splanchnic mesoderm will form the heart
    - The somatic mesoderm will form the body cavity wall

The cranial and caudal ends of the primitive streak undergo a fusion between the ectoderm and endodermal layers, forming bilaminar membranes, the cranial membrane is known as the oropharyngeal membrane and the caudal membrane is known as the cloacal membrane.

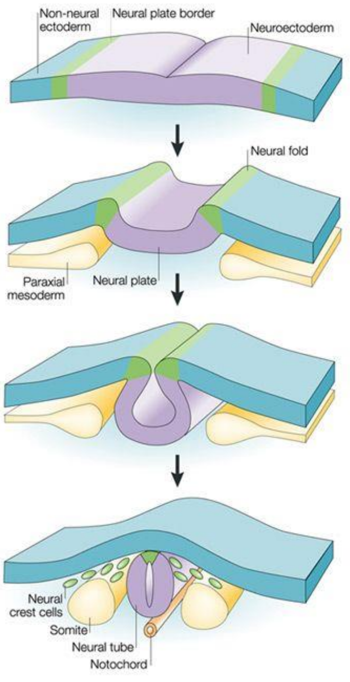


NEURULATION

The midsagittal region of the ectoderm become specialized to form the neural plate under signalling from the notochord. The cells to either side of the neural plate become the neural crest.

- This plate of tissue invaginates to form the neural crest and eventually pinches off to form the neural tube.
- The neural crest cells also separate and migrate between the neural tube and the ectoderm to form neural crest cells
    - The neural crest cells eventually migrate bilaterally to the neural tube to form spinal ganglion

The neural tube will go on to form the central nervous system, while the neural crest cells will form components of the peripheral nervous system.



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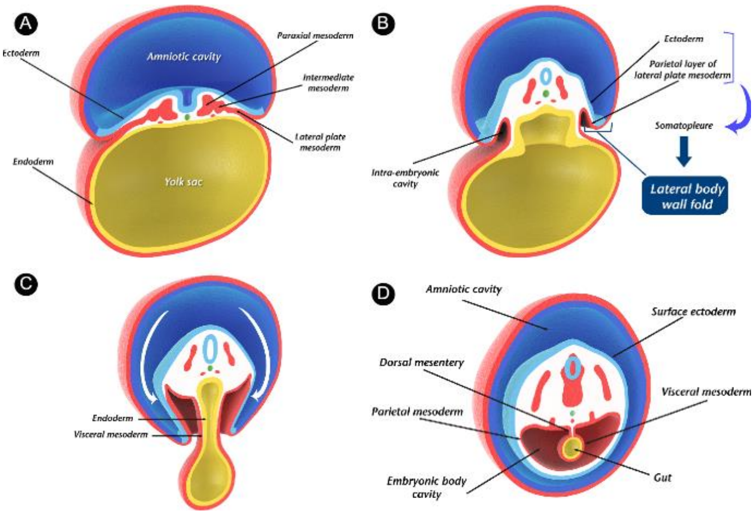
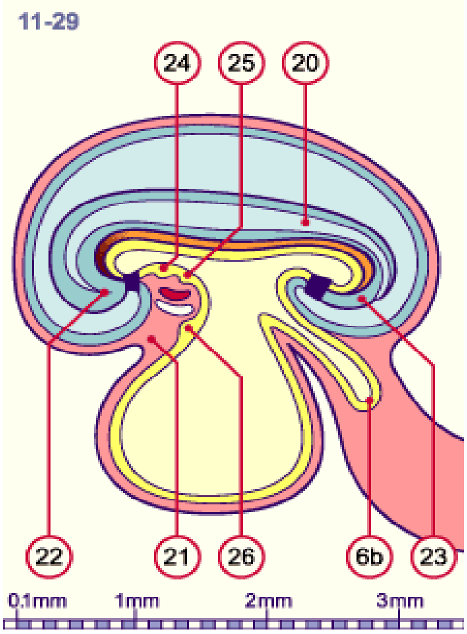
BODY FOLDING

The developing embryo begins as a flat oval shaped structure and must undergo folding processes to assume its final shape. This involves:

- Cranial rostral flexion: the head flexes inwards
    - This brings the cardiogenic area of the developing embryo, the future mouth and pharynx area in front of the developing neural tube
    - This occurs because of the forebrain overgrows the cranial structures forcing a 180-degree rotation
- Tail caudal flexion: the tail of the embryo flexes inwards
    - This allows for the connecting stalk of the extraembryonic coelom to become relocated next to the yolk sac
        - The root of the connecting stalk contains the allantois
    - This occurs because the caudal end of the neural tube outgrows the rest of the body
- Bilateral folding: the development of the mesoderm causes the lateral sides of the body to fold inwards
    - This folding inward causes yolk sac to be formed into the gut tube and pinched off in all areas except at the umbilical region
        - This connecting stalk eventually thins and is called the Vitelline duct
    - The intraembryonic coelom is formed from the fusion of the somatic and splanchnic mesoderm bilaterally above and below the connecting stalk





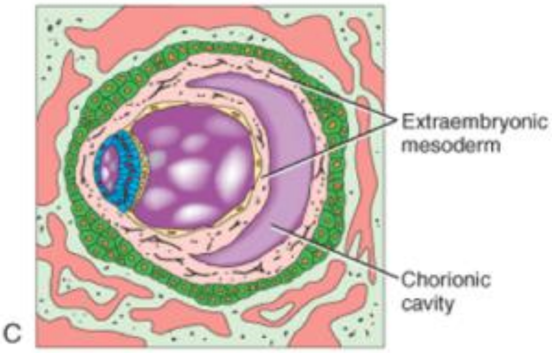
FORMATION OF THE PLACENTA

The trophoblast cells differentiate into the syncytiotrophoblast and the cytotrophoblast

- The syncytiotrophoblast is a multinucleated syncytium that makes up the outer layer; the individual cells lose their cell membranes and become connected
    - The syncytiotrophoblast releases hydrolytic enzymes that allow for continual implantation and growth of the embryo
    - The spaces between the growing fingers of syncytiotrophoblast are called lacunae
    - The proteolytic enzymes break down the blood vessels and allows for the lacunae to become filled with blood (known as intervillous spaces) – this occurs around day 9
- The cytotrophoblast is the inner layer of cells
- By day 10, the endometrium fully encloses the developing blastocyst, with a coagulation plug forming at the point of initial implantation. At this point, the endometrium becomes known as the decidua. The decidua is a specialised endometrium that stored nutrients under the influence of progesterone. This is essential for the survival of the blastocyst.

Around the same time in the middle of the second week, the inner trophoblast, outer amnion and the yolk sac become lined by extraembryonic mesoderm produced by the hypoblast.

- The extraembryonic mesoderm splits into two and forms the extraembryonic coelom or the chorionic cavity
    - This coelom separates the embryo from the outer wall of the blastocyst (this will become the chorionic cavity)
    - The outer layer against the cytotrophoblast is called the somatic extraembryonic mesoderm
    - The inner layer against the embryo is known as the splanchnic extraembryonic mesoderm
    - The two layers are connected via the connecting stalk



12-13 days

Schoenwolf et al: Larsen's Human Embryology,
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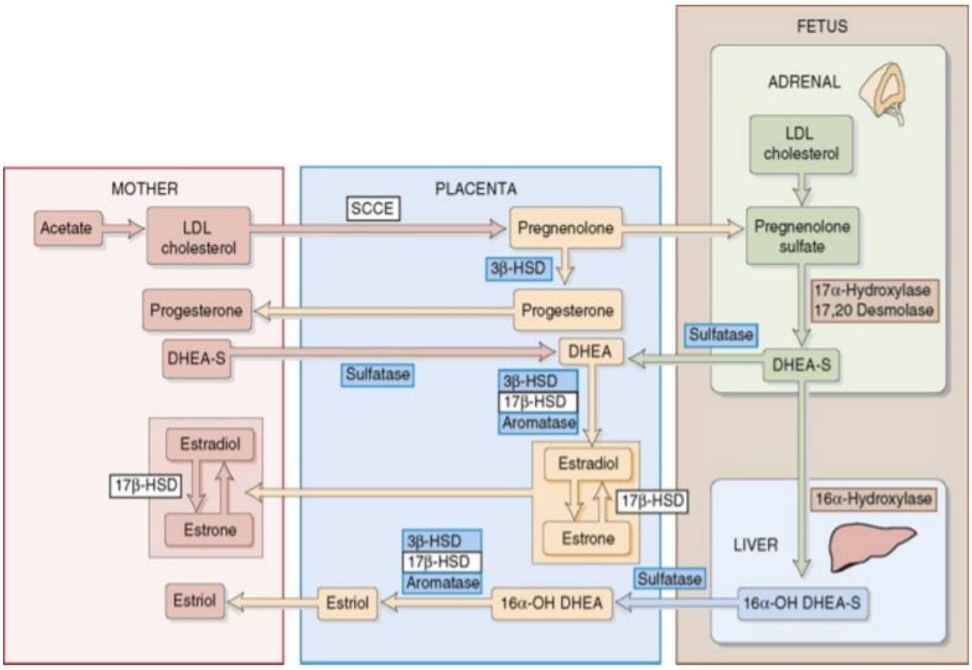
Cytotrophoblast cells continually differentiate into villous and extravillous trophoblast. They penetrate through the syncytiotrophoblast and move outwards and around the intervillous spaces.

- Primary villi form (formed from cytotrophoblast cells) extending from the inner cytotrophoblast to the outer cytotrophoblast shell
- Throughout week three the somatic extraembryonic mesoderm enters the villi to form secondary villi
- Extraembryonic mesodermal cells within the villi start forming chorionic arteries and cotyledon capillaries to form villous capillaries. This forms the tertiary chorionic villi.
    - The capillaries are connected to the developing embryo via the umbilical cord arteries (2x) and vein
    - This occurs at the chorionic plate

By the end of week three, the exchange system between the maternal and foetal circulation is established. This is maintained until around weeks 15-20 when the cytotrophoblastic cells and some mesoderm regress. This forms the hemochorial placenta; the chorion is in direct contact with the blood supply. The initial diffusion barrier consists of:

- Syncytiotrophoblast

- Cytotrophoblast
- Chorionic lamina
- Blood vessels



Throughout weeks four to eight the villi become more branched to increase the surface area. These together create the chorionic frondosum layer. This is attached to the decidua basalis with intervillous spaces. These two structures create the placenta. On the outer surface of the developing baby is known as the decidua capsularis, while the opposite side of the uterus without any attachment is known as the decidua parietalis.

By the fourth- or fifth-month placental fissures begin to form, growing inwards into the intervillous spaces. This separates some of the tertiary villi into separate areas. These are known as cotyledons.

The mature placenta is responsible for the transfer of nutrients and removal of waste from the developing foetus. This can occur via simple diffusion, facilitated diffusion, active transport and pinocytosis.

The placenta, along with the foetus and the mother, is responsible for steroid hormone synthesis throughout pregnancy. This is because the maternal body contains the required substrates but does not have the capacity to produce adequate levels of the hormone without placental input. Steroid hormones are also extremely important in the development of the baby.

Other important factors originating from the placenta include:

- hCG
- Human chorionic somatomammotropin
- Placental CRH

SEX DIFFERENTIATION

The primordial germ cells of the embryo migrate from the yolk sac, through the umbilical cord and to the gonadal ridge of the mesoderm around week 5-6. They are originally endodermal in origin.

The intermediate mesoderm condenses into cylindrical structures known as the urogenital ridge. The gonadal ridge of the embryo is a part of the urogenital ridge which is in close relation to the mesonephric and paramesonephric duct as well as the developing kidney and urinary structures. Endodermal cells in the yolk sac differentiate into primordial germ cells.

- The primordial germ cells come to occupy the space lateral to the mesonephros known as the gonadal ridge
    - The mesonephros is the transitory kidney, the second of three kidney development stages in the embryo
- The primordial germ cells are surrounded by somatic support cells that will develop the other tissues of the gonads

The first stage of sex development involves the chromosomal sex of the foetus. XY children will become male and XX children will become male. This is because of the male genes contained in the Y chromosome.

- The SRY (sex determining region of the Y chromosome) codes for TDF (testes determining factor)
- TDF is expressed in the somatic support cells in XY embryos, causing the cells of the gonads to form testes
    - This is known as primary sex determination
    - If SRY and TDF are absent, female development will occur
- This causes the mesoderm of the undifferentiated gonads to form medullary cords, carrying the primitive germs cells into the centre of the gonad
    - These then develop into the straight tubules, seminiferous tubules and the rete testes
- The epithelial layer of the gonads becomes thins and develops into the tunica albuginea
- In a female, the undifferentiated gonads develop into ovaries via sex cord development and regression
- This is followed by the development of cortical cords which develop into nests of follicular cells that surround the primordial germ cells
    - This forms the primordial follicle
        - The primordial germ cell develops into an immature oocyte during foetal life but are halted in meiosis I until puberty

The second stage of development involves the determination of the gonadal sex.

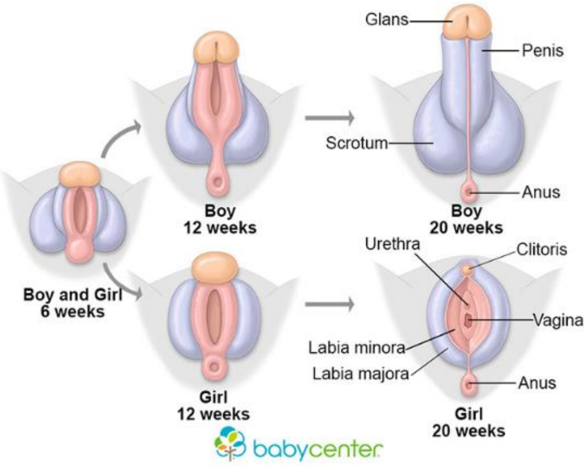
- In XY embryos, the SRY and TDF will cause the differentiation of the somatic support cells into testes
- Testes contain Sertoli cells which produce Anti-Mullerian Hormone (AMH)
    - AMH causes the regression of the paramesonephric duct
    - Sertoli cell interaction also ensures the primordial germ cells do not enter development yet
- Testes also contain Leydig cells which produce testosterone
    - Testosterone ensures the development of the mesonephric duct
- In the absence of SRY and TDF and in the presence of pro-ovarian factors, the somatic support cells differentiate into ovaries and follicular cells begin to develop
    - Absent testosterone causes the regression of the mesonephric duct
    - Absent AMH causes the Mullerian duct to be maintained

In the male, the mesonephric duct will form:

- The duct of the epididymis
- The efferent ductules
- The ductus deferens
- The ejaculatory ducts
- The seminal vesicles

In the female, the paramesonephric duct will form:

- The uterine tubes
- The uterus
    - This occurs via the fusion of the lower parts of the paramesonephric duct
- The cervix
- The vagina (upper 1/3)
    - The lower 2/3 develops from the urogenital sinus



The development of the external genitalia is the final step in sex differentiation, and many aspects of secondary sexual characteristics go on to develop after birth. In the embryo, the genitals are bi potential, consisting of a genital tubercle, labioscrotal swelling, anus and urethral folds around a urethral groove.

- In the male, the genital tubercle elongates and forms the glans penis and the body of the penis, while the labioscrotal swellings drop to form the scrotum.
    - The urethral groove fuses and closes on the back side of the penis as it elongates, allowing the urethra to be enclosed within the penis
    - This is largely controlled by the influence of testosterone
        - More specifically it is caused by the DHT formed by 5-alpha reductase in the male genital region
- In the female, the genital tubercle forms the glans clitoris by regressing slightly and the labioscrotal swellings form the labia majora and mons pubic via fusion of their anterior portion.
    - The urethral folds form the labia minora
    - The labia minora open around the vestibule of the vagina, which is a common opening for both the vagina and the urethra in females

Gonadal descent occurs differently in male and female embryos. In both the male and female, the gonads are attached at the superior pole to the craniosuspensory ligament and inferiorly to the gubernaculum. The gubernaculum is attached to the labioscrotal swellings inferiorly in both males and females.

- In males, androgens cause the degeneration of the CSL, allowing the gubernaculum to guide the testes downwards and into the scrotum throughout development
- In females, the gubernaculum degenerates while the CSL is maintained. There is a slight change in the position of the gonads but they do not descend the entire length.

DEVELOPMENT OF TWINS

All monozygotic twins arise from a single fertilized ovum. Dizygotic twins arise when two eggs are ovulated, fertilised and carried to term. A small minority are monozygotic, which comes from a single fertilised egg that separates into two embryos early in development. This can occur any time from the 1st to 13th days of development and the stage at which it occurs will determine how the embryos develop.

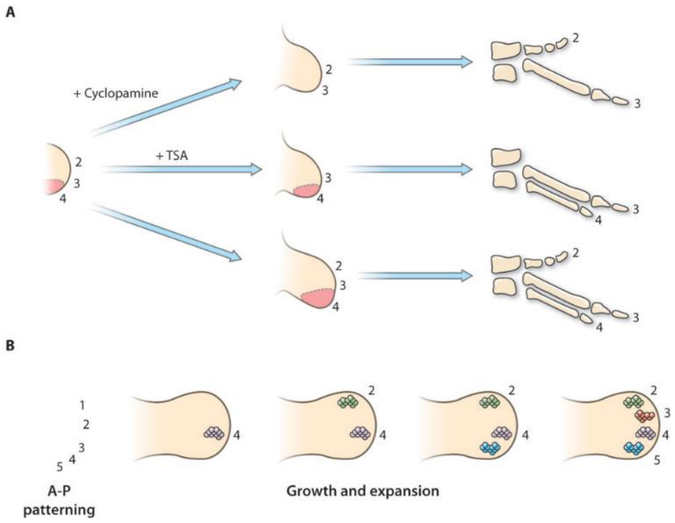
- Early embryo splitting results in two discrete embryos that can implant separately and form two individual conceptions
    - These twins are known as dichorionic, diamniotic twins
        - Split must occur 2-3 days after fertilization (before the development of the trophoblastic layer etc)
- The early embryo can split and then refuse again
    - These embryos will have their own amniotic cavity but share a chorionic placenta
- Monochorionic and di-amniotic twins are formed by slightly later splitting
    - The trophoblast has already differentiated so the foetuses share a placenta but have different amniotic sacs
- Monochorionic and monoamniotic twins are formed when the splitting occurs later in development
    - This occurs after 8-13 days of fertilisation
- Conjoined twins can be formed when the splitting occurs extremely later

DEVELOPMENT OF THE LIMBS

Development of the limbs and body shape is determined by the Sonic Hedgehog protein (SHH protein). All stages of limb develop with the upper limb buds before the lower limb buds. By the end of week 4, limb buds are visible on the ventrolateral body wall. The limb buds are composed of an ectodermal cover, a myotome muscle structure and a mesenchymal core.

- The limbs are derived from dorsolateral cells of somites (myotomes) derives from paraxial mesoderm – skeletal muscle and lateral plate mesoderm – gives rise of connective tissue, bones and cartilage
    - C4-T2 migrate to form upper limb
    - L2-S2 migrate to form the lower limb
- The apical ectodermal ridge is a thickening of the ectoderm covering a core of proliferating mesoderm
    - The AER signals to the underlying mesoderm which is necessary for limb development
        - If the AER is removed the limb bud stops developing
- The limb buds extend to form a hand plate and foot plate
    - Each hand and foot plate have small rays of tissue (digital rays)
        - Tissue between the rays will undergo apoptosis to form fingers and toes
- SHH (sonic hedgehog proteins) are involves in determining the digit formation

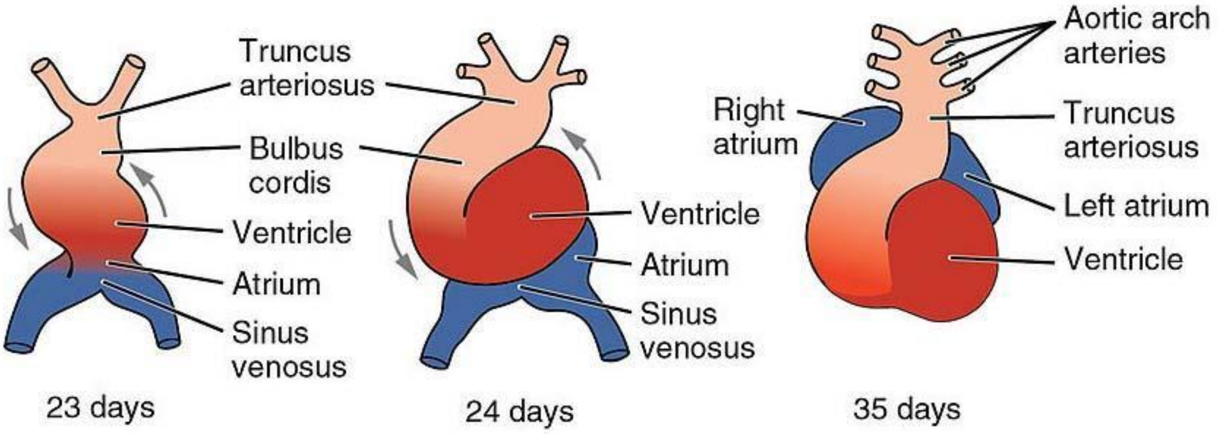
    - The gradient and exposure gene of SHH from the AER cause the development of the different fingers and toes
    - The zone of polarising activity or ZPA is the region underneath the AER at the posterior aspect of the limb bud and influences the AER
        - This is responsible for the anteroposterior pattern of digit formation
    - The ZPA produces retinoic acid and this initiates the SHH production in a gradient
- Chondrification of the limbs begin
- The upper and lower limb undergo rotation
    - Upper limb rotates to have flexor muscles anterior and extensor muscles posteriorly
        - Elbow points posteriorly
    - Lower limb rotates to have flexor muscles posteriorly and extensor muscles anteriorly
        - Knee points anteriorly
- Ossification begins



DEVELOPMENT OF THE HEART

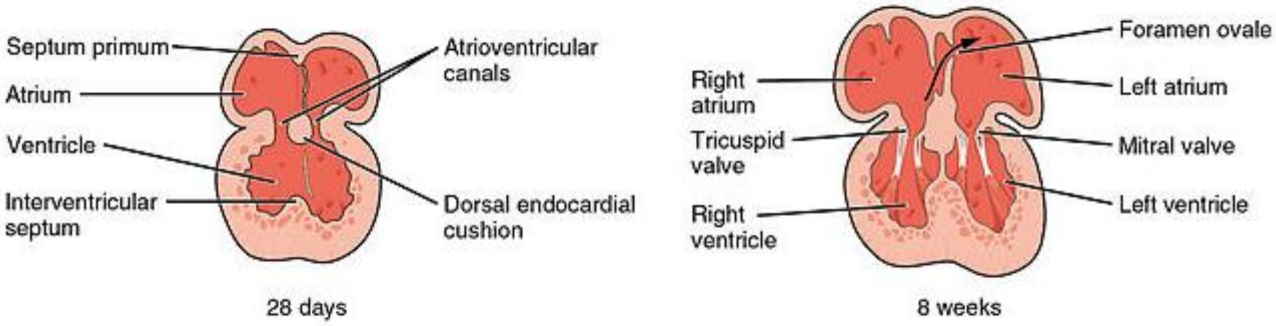
The CV system begins to develop around week three of development (around the time of bilaminar germ disc). As the trilaminar germ disc forms during gastrulation the visceral mesoderm forms, from which the heart is derived.

- The primary heart field develops at the top of the cranial end of the trilaminar germ disc embryo
- The cells of the heart field organise themselves into two heart tubes, growing in the caudal direction
    - The heart tubes are connected to the vitelline vein which is connected to the yolk sac, from which the blood is originally derived
    - There is two dorsal aortae through which blood exits the heart tubes
- Body folding causes the fusion of the two heart tubes in the anterior aspect of the embryo
    - This forms a single heart tube
    - The left and right vitelline veins to which the tubes were connected fuse to form the sinus venosus (inflow tract)



    - The two dorsal aorta fuses to form the aortic sac (outflow tract)
- Craniocaudal folding occurs and pushes the heart tube to the chest area
- The heart tube develops into sections:
    - Sinus venosus with left and right sinus horn
    - Primitive atrium
        - Forms left and right atria
    - Primitive ventricle
        - Atrium and ventricle are separated by AV sulcus
        - Form the left ventricle
    - Bulbus cordis
        - Separated from the primitive ventricle by the bulboventricular sulcus
        - Forms the right ventricle and outflow tracts
    - Truncus arteriosus
    - Aortic arches
- Looping of the heart tubes occurs: it becomes longer, the walls become thicker and it rearranges itself
    - Initial movement involves the formation of a C shape but the downwards and rightwards movement of the bulbus cordis and truncus arteriosus and the ventricle moves to the left and to the front and the primitive atrium moves backwards and upwards
    - The primitive ventricle moves to the left, crossing over the midline again and in front of the primitive atrium
- The mesoderm proliferates on the anterior and posterior aspects of the heart tube to form an endocardial cushion which grow towards one another and fuse
    - This separates the heart into left and right atrioventricular canals
- Endocardial cells proliferate to form the leaflets of the mitral and tricuspid valves
    - This divides the atria from the ventricles
- The septum primum grows downwards between the L and R atria

    - There is initially a hole known as the ostium primum between the L and R atria
- The septum primum fuses with the endocardial cushion and closes the gap between L and R atria
- A hole appears in the upper area of the septum primum
    - This is known as the ostium secondum
- The septum secondum grows downwards to the right of the septum primum to cover the ostium secondum and leaving a small hole known as the foramen ovale
    - This allows blood to flow from the left to the right atrium during foetal life



- A muscular ridge of tissue grows upwards from the apex of the heart and fuses with a membranous region descending from the endocardial cushion
    - This forms the L and R ventricles
- The truncus arteriosus divides into the aorta and pulmonary artery
    - Cardiac cushions grow with a spiralling trajectory and wrap around each other to form the aorticopulmonary septum
- The semilunar valves develop shortly after
- The sinus venosus becomes asymmetrical and shifts to the right
    - The right horn becomes the openings of the inferior and superior vena cava
    - The left sinus horn shrinks and becomes the coronary sinus

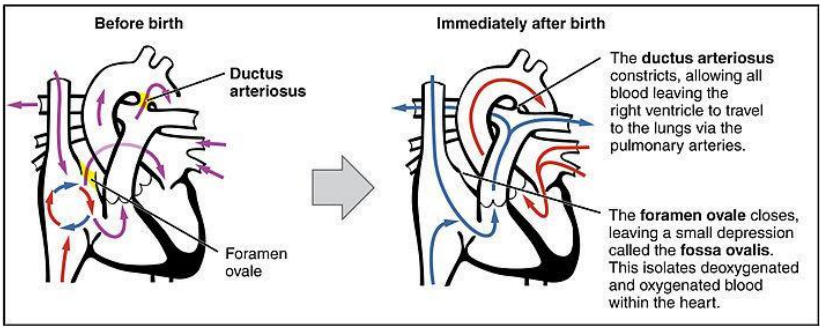
FOETAL CIRCULATION

The foetal circulation has four special adaptations that allow it to deal with the environment of the uterus. The lungs are immature and under high pressure as well as hypoxically vasoconstricted, while oxygenation of the blood occurs in the placenta.

- Umbilical veins and arteries
    - The umbilical vein carries oxygenated blood towards the body and liver
    - The internal iliac arteries give rise to an umbilical artery which move deoxygenated blood to the placenta
- Ductus venosus
    - Connects the left vein to the IVC of the baby to bypass the liver circulation
    - This mixes oxygenated blood from the IVC with oxygenated blood of the umbilical vein
- Foramen ovale
    - Opening between the L and R atrium
    - Moves blood from the RA (high pressure) to the LA (low pressure)
        - Most of the blood from the RA bypasses the lungs and the RV entirely
- Ductus arteriosus
    - Connects the pulmonary artery and the aorta
    - Shunts blood from the high-pressure pulmonary artery to low pressure aorta

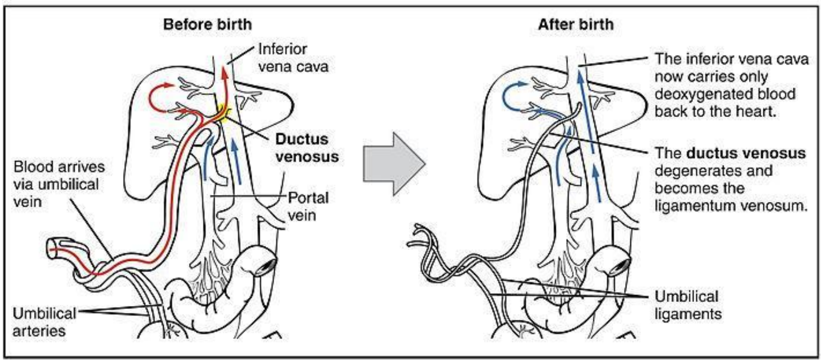
After birth, lungs are filled with air and hypoxic vasoconstriction is reduced, reducing the pressure in the right side of the heart. The left side of the heart is under greater pressure.

- The foramen ovale tissue is pushed in the opposite direction initiating functional closure, which develops into physiological closure over time, of the foramen ovale
    - Forms the fossa ovalis
- Higher oxygen levels cause the SM of the ductus arteriosus to constrict
- Placenta is separated and prostaglandin levels pass
    - These two factors contribute to the closure of the ductus arteriosus
    - Forms ligamentum arteriosum
- Umbilical arteries involute
- Umbilical vein blood flow clots and stops
    - Forms the round ligament of the liver
- Ductus venosus blood flow clots and stops
    - Forms the ligamentum venosum of the liver



The **ductus arteriosus** constricts, allowing all blood leaving the right ventricle to travel to the lungs via the pulmonary arteries.

The **foramen ovale** closes, leaving a small depression called the **fossa ovalis**. This isolates deoxygenated and oxygenated blood within the heart.



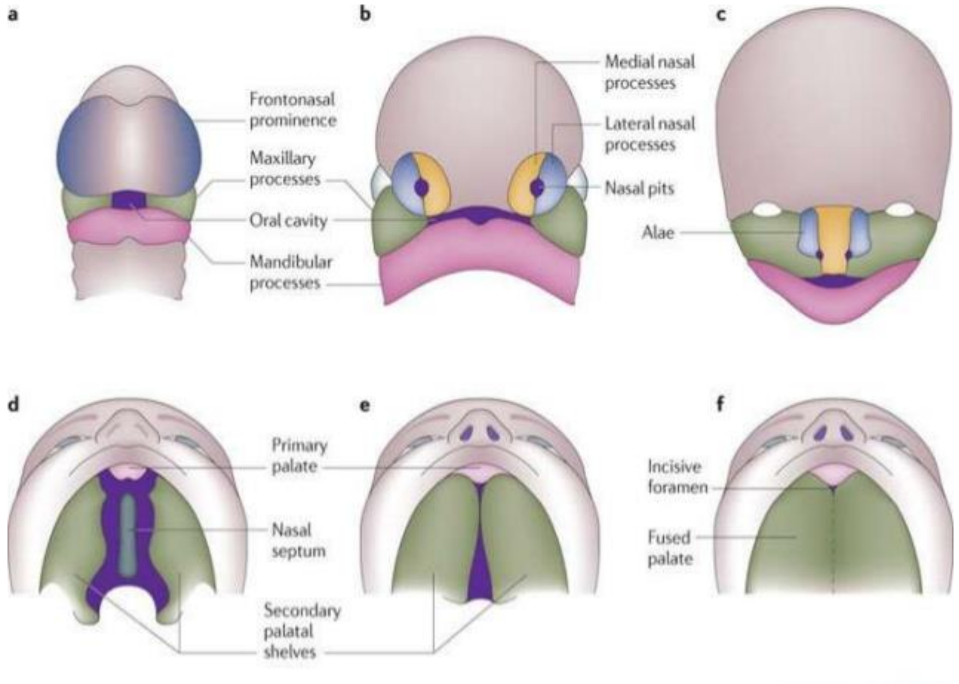
The inferior vena cava now carries only deoxygenated blood back to the heart.

The **ductus venosus** degenerates and becomes the ligamentum venosum.

DEVELOPMENT OF THE FACE

At week four of development the pharyngeal apparatus begins to develop, consisting of the pharyngeal arches, pouches and clefts. The paired pharyngeal arches develop from mesoderm. The four pharyngeal clefts form on the outside of the pharyngeal arches from ectoderm, and four pharyngeal pouches develop on the inside from endoderm.

- Each pharyngeal arch and its associated cleft and pouch carry a cranial nerve which will innervate it's future structures
  - 1st pharyngeal arch: trigeminal nerve mandibular arch – all the structures associated with chewing
    - Maxilla and mandible
    - Incus and malleus of the ear
    - Temporal bones
    - Zygomatic bones
    - Maxillary and mandibular prominences
    - Temporalis, masseter and pterygoid muscles
    - Mylohyoid muscles
    - Anterior belly digastric muscle
  - 2nd pharyngeal arch: facial nerve – forming facial expressions
    - Hyoid bone
    - Styloid process of temporal bone
    - Stapes
    - Posterior belly digastric muscle
    - Stylohyoid muscle
  - 3rd pharyngeal arch: glossopharyngeal nerve
    - Stylopharyngeus
    - Hyoid bone
  - 4th and 6th arches: Vagus nerve (superior laryngeal: 4th, recurrent laryngeal: 6th)
    - Laryngeal cartilages
    - Levator palatini
    - Pharyngeal constrictors
    - Cricothyroid muscle
    - Intrinsic muscles of the larynx



Nature Reviews | Genetics

Many of the features of the face originate from cranial neural crest cell which have migrated from the neural tube.

By the fifth week of the development there are five facial swellings formed:

- The frontonasal prominence
- The paired maxillary prominences
- The paired mandibular prominences

The nasal placodes (will form the olfactory system) and the optic placodes (will form the visual system) will form during the 5th week.

- By week 6 the nasal placode develops a depression at its centre called the nasal pit
  - This will form the nostril
- The nasal placode can be divided into a lateral nasal process and a medial nasal process after the formation of the nasal pit
  - The lateral nasal processes will form the ala of the nose
  - The medial nasal processes will form the bridge of the nose
- During week 7 the two medial nasal processes grow larger and inwards to fuse and grow downwards to form intermaxillary segment
  - This will go on to form the philtrum of the upper lip and the medial part of the maxillary bone
- The maxillary prominence also fuses with the medial nasal process after the development of the intermaxillary segment
  - The maxillary prominences on either side of the intermaxillary segment will form the lateral parts of the maxillary bone

The maxillary and mandibular prominences enlarge, grow forward and towards one another.

- These will eventually give rise to the upper and lower jaws
- By week 6, the mandibular prominences have fused
  - This goes on to form the lower lip, lower jaw etc.
- By week 7, the maxillary prominences grow and fuse with the intermaxillary segment to form the upper lip and jaw architecture
  - By week 10 the intermaxillary process forms the philtrum of the upper lip

Merging of the maxillary and mandibular prominences forms the cheek and corners of the mouth.

The secondary nasal palate is formed from palatal shelves that grow medially from the maxillary swellings. Palatal shelves initially grow on the inferior side of the tongue but rotate upwards to meet in the midline superior to the tongue. They will fuse with one another here.

The nasal septum grows in an anterior-inferior direction and separates the node into left and right passages.

The natal septum will fuse with the fused palatal shelves.

DEVELOPMENT OF THE BODY WALL AND CAVITIES

The endoderm gives rise to the lining of the gut tube. Around day 19 a space forms in the lateral plate mesoderm known as the intra-embryonic coelom which separates the lateral plate mesoderm into:

- Dorsal (parietal) lateral plate mesoderm
  - Attached to ectoderm and wraps around amnion
    - Gives rise to serous membranes that line cavities
- Ventral (visceral) lateral plate mesoderm
  - Attached to the endoderm and covers the yolk sac
    - Gives rise to serous membrane of lungs, heart and abdominal organs

During the fourth week body folding forms a primitive gut from the endoderm and yolk sac. During this process the combined parietal mesoderm and ectoderm fold down at the amnion. These layers eventually merge at the front of the embryo to become the anterior body wall. The connecting stalk that attaches the yolk sac to the gut tube is renamed the vitelline duct.

- Double layered mesoderm forms the dorsal mesentery which suspends the gut tube in the embryo
- Around day 22 the septum transversum forms cranially to the vitelline duct and divides the thoracic and abdominal cavity as it develops

More membranes will develop to divide the thoracic cavity into pleural and pericardial regions, while the muscular and tendinous components of the diaphragm will develop from the 3rd, 4th and 5th somites and the mesoderm of the lumbar column respectively.

PHYSIOLOGY OF PREGNANCY

Pregnancy causes many physiological changes to the mother's body that allow her to cope with the growth of the foetus and make the uterus an ideal position for the foetus growth.

Many of these changes are driven by hormones.

- hCG
- Oestrogen: helps to prepare the body for birth by inducing oxytocin receptors in the endometrium and the uterus
- Progesterone: helps with the maintenance of the endometrium and prepares the mammary glands for lactation

Prior to the formation of the placenta, the corpus luteum is the primary source of these hormones. After week 13 of pregnancy the placenta is responsible for the production of these hormones.

Haematological changes include:

- Increased plasma volume by up to 40%
- Increased in RBC volume by up to 25%
- Increased clotting factors after birth
  - Prevents excessive bleeding post-partum
  - Produces a hypercoagulable state
- Increased plasma volume and RBC volume can contribute to oedema

Cardiovascular changes include:

- Increased cardiac output due to increased heart rate and stroke volume
- Prostaglandins cause decreased vascular resistance
- Physiological hypertrophy of the heart
  - This usually returns to normal after birth
- Drop in blood pressure is normal due to a decreased systemic vascular resistance
  - Can result in hypotension
- Baby compresses IVC and decreases venous return to the right atrium and pelvic veins can be compressed
  - Can cause varicose veins

Renal changes:

- Increased cardiac output causes increased blood flow to the kidneys and results in GFR
  - Increased urinary output
    - This can be compounded in later pregnancy because of compression of the bladder
  - Increased size of kidney pelvis, calyces, ureters
- Hypomobility of the ureter causes increased risk of UTI

Respiratory changes:

- Increased intrabdominal pressure results in increased diaphragmatic breathing
- Increased rate of breathing, hyperventilation, tidal volume etc
  - This causes decreased CO2 and a milk respiratory alkalosis
    - This is used to enhance across the placenta

Digestive changes:

- Progesterone causes lower oesophageal sphincter relaxation
- Intraabdominal pressure increases
  - These two together can cause reflux
- Progesterone causes reduced bowel motions and constipation

Musculoskeletal changes:

- The uterus size increases causing lordosis and back pain
- There is an increased progesterone level which causes increased risk of strains and sprains, unstable pelvic gait etc.
  - This also allows for relaxation of the ligaments of the respiratory system which allows for further lung expansion

Endocrine changes:

- Oestrogen, progesterone, hCG increase
- Human placental lactogen increases
  - Lipolytic effect to increase FFA for the mother and glucose availability for the baby
    - Diabetogenic

- Increased thyroid hormone activity
    - Increases BMR to meet metabolic demands
- Most anterior pituitary hormone levels are increased

Metabolic:

- Increased protein, fat deposits
- Increased blood lipid
- Increased salt accumulation
    - Promotes water retention
- Increased body weight

Reproductive changes:

- Breast enlargement and development
- Areolar and linea alba pigmentation occur
    - This occurs due to increased levels of ACTH and MSH
- Uterus undergoes hypertrophy
    - Particularly in the superior aspect

Emotional changes:

- Progesterone and oestrogen can contribute to mood changes
    - This can range from mild to severe
- Mental fogginess and reduced concentration

Immunological changes:

- Implantation and placentation is pro-inflammatory:
    - This process resembles tissue injury and repair and thus inflammation and mediators are present
        - This results in increased number of adhesive molecules and removal of mucins to allow for blastocyst adhesion
- Majority of pregnancy is anti-inflammatory
    - Inflammation is negative for a baby's health and development thus there is a symbiosis between the mother and the foetus during the majority of pregnancy
- Labour is pro-inflammatory:
    - There is an influx of immune cells to the myometrium which then and their products promoting contraction
        - This allows for the delivery of the baby and separation of the placenta

The health of the women and foetus is routinely monitored in antenatal care to assess risk. This involves a wide range of measures including:

- Personal and family history, with specific attention on previous pregnancies or pathologies related to pregnancy
- Blood pressure: particularly important in assessment for pre-eclampsia
- Weight
- Laboratory analysis
    - CBC
    - Haemoglobin
    - Blood typing (including Rhesus D)
        - Rhesus negative mothers are given prophylactic anti-D immunoglobulins ar 28 weeks (regardless of baby's type) to prevent alloimmunization
    - Urine dipstick
        - Proteinuria is key measurement for pre-eclampsia
    - Urine culture: STI screening
- STI screening: particularly testing for syphilis, HIV, Hepatitis B,m chlamydia
- Screening for cystic fibrosis, fragile X syndrome and muscular atrophy
- Immunity to rubella, varicella
- Investigate and manage pre-existing pathologies and medications
- Ultrasound to investigate:
    - Gestational age
    - Placental pathologies
    - Congenital malformations
- Variety of tests for chromosomal or genetic abnormalities
    - Screening tests include NIPT and ultrasounds while diagnostic tests include amniocentesis and CVS which are only conducted in high risk cases as they have associated risks
- Group B strep screening: 25-37 weeks gestation
- OGTT to investigate for gestational diabetes
- Ensure CST is current
- Ask about movement of baby/check heartbeat
- Enquire about women's wellbeing and coping

Generally, all women are given routine flu vaccination and Boostrix. They are also advised to follow:

- Avoidance of saunas
- Supplemental folate
- No smoking or drinking
- Iodine rich foods
- Avoid X-rays
- Regular moderate exercise

Throughout the labour the mother is monitored and given pain relief as necessary. Key measurements include pulse, temperature, blood loss etc. The active management of labour is used to prevent pathologies of both mother and foetus.

NUTRITION DURING PREGNANCY

The key features of nutritional recommendations during pregnancy include:

- Eating the recommended number of serves of food groups
- Having small amounts of caffeine
- No smoking and/or drinking and/or illicit substance use
- Do not undertake weight loss diets
- A small amount of weight gain is expected
    - The amount of weight gain acceptable will depend on the pre-pregnancy BMI
    - The additional energy requirements during pregnancy equate to around an extra 300 calories per day; this is the same as around a piece of fruit and a sandwich
- Supplementation with folic acid and iodine
    - These should be commenced before conception if possible
    - Deficiency can cause NTD (folate) or cognitive and mental impairment (iodine)
- Iron supplementation can be used in iron-deficient women
    - Blood volume during pregnancy can increase by 50%
    - Deficiency can cause intra-uterine growth restriction, low birth weight and perinatal mortality
    - Anaemia can compromise oxygen delivery to the foetus
    - The absorption of iron from the gut during the third trimester of pregnancy is insufficient to meet daily need despite supplementation; this means that women are reliant on body stores prior to pregnancy
- B vitamin supplementation may be needed in vegan or vegetarian women but not usually in the wider population
    - Deficiency is rare as it may contribute to infertility
- Vitamin D supplements can be used to maintain maternal calcium homeostasis
- Protein requirements are around 21 grams/day
    - Deficiency of iron can lead to foetal growth delay, low birth weight and perinatal mortality
- Fatty acids are essential, particularly 6 and 3
    - Deficiencies are rare but can cause low birth weight, early delivery and impaired brain, nervous system and visual development
- Carbohydrate intake is important: fluid requirements increase, and low carb diets can cause fluid loss
    - The impact of a ketogenic diet has not been studied in pregnancy
- There is no additional need for calcium during pregnancy

Nutrition is also important pre-pregnancy and can impact male and female fertility. Healthy weight range allows for the best pregnancy chance; every BMI point above 29 causes a 4% reduction in fertility.

Food safety is important during pregnancy because of the potential risks to health. Key infections include listeria which can be obtained by processed deli meat, soft cheese, uncooked seafood, pre-packaged salads and fruits etc. Women should also avoid raw or partially cooked eggs to avoid salmonella, undercooked meats to avoid toxoplasmosis and liver products to avoid vitamin A toxicity.

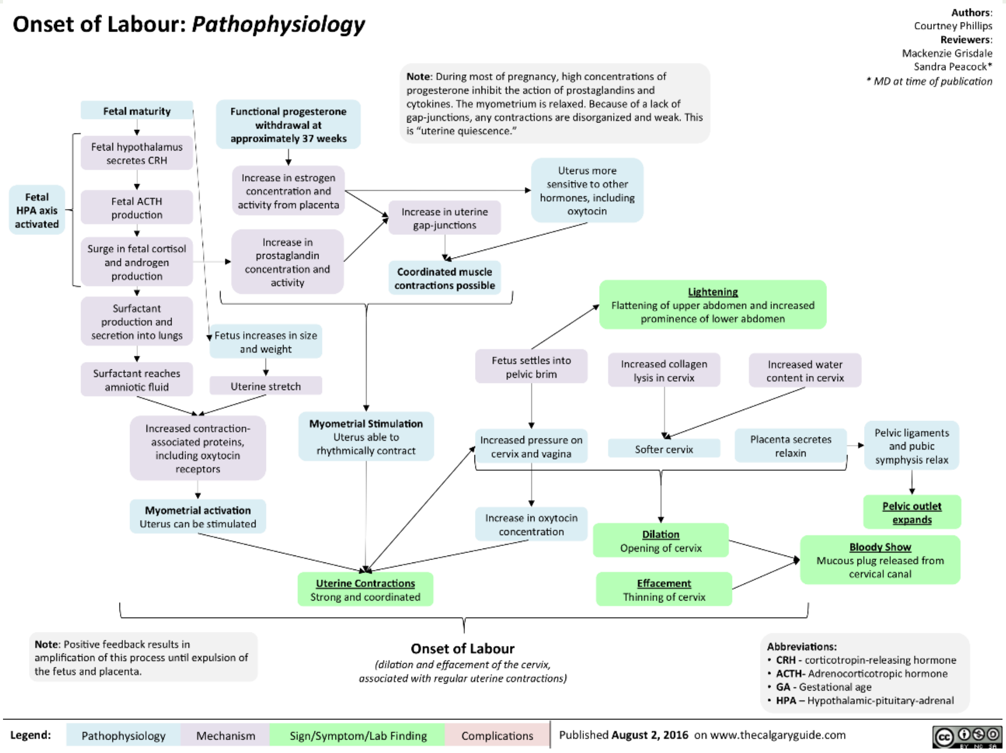
Nutritional requirements stay elevated, although not by as much during the breastfeeding period.

Breast feeding can also contribute to port-partum weight loss, a reduction in T2DM risk and osteoporosis. Women should not exclude allergenic foods during the breastfeeding age.

Nutrition of the infant:

- Breastfeeding is recommended for 6 months minimum
- Regular cow's milk avoided until 12 months
- Introduction of solid foods can occur between 4-6 months of age
- Introduction of common food allergens can be done during this period unless prior allergy is established
- Hydrolysed infant formula is not recommended if at all possible

LABOUR



Onset of Labour: ***Pathophysiology***

Authors:
Courtney Phillips
Reviewers:
Mackenzie Grisdale
Sandra Peacock*
** MD at time of publication*

Note: During most of pregnancy, high concentrations of progesterone inhibit the action of prostaglandins and cytokines. The myometrium is relaxed. Because of a lack of gap-junctions, any contractions are disorganized and weak. This is "uterine quiescence."

Fetal maturity
Functional progesterone withdrawal at approximately 37 weeks
Fetal hypothalamus secretes CRH
Fetal HPA axis activated
Fetal ACTH production
Surge in fetal cortisol and androgen production
Increase in estrogen concentration and activity from placenta
Increase in prostaglandin concentration and activity
Increase in uterine gap-junctions
Uterus more sensitive to other hormones, including oxytocin
Coordinated muscle contractions possible
Surfactant production and secretion into lungs
Surfactant reaches amniotic fluid
Fetus increases in size and weight
Uterine stretch
Lightening
Flattening of upper abdomen and increased prominence of lower abdomen
Fetus settles into pelvic brim
Increased collagen lysis in cervix
Increased water content in cervix
Increased contraction-associated proteins, including oxytocin receptors
Myometrial Stimulation
Uterus able to rhythmically contract
Increased pressure on cervix and vagina
Softer cervix
Placenta secretes relaxin
Pelvic ligaments and pubic symphysis relax
Pelvic outlet expands
Myometrial activation
Uterus can be stimulated
Increase in oxytocin concentration
Dilation
Opening of cervix
Bloody Show
Mucous plug released from cervical canal
Uterine Contractions
Strong and coordinated
Effacement
Thinning of cervix

Note: Positive feedback results in amplification of this process until expulsion of the fetus and placenta.

Onset of Labour
(dilation and effacement of the cervix, associated with regular uterine contractions)

Abbreviations:
- **CRH** - corticotropin-releasing hormone
- **ACTH-** Adrenocorticotropic hormone
- **GA** - Gestational age
- **HPA** – Hypothalamic-pituitary-adrenal

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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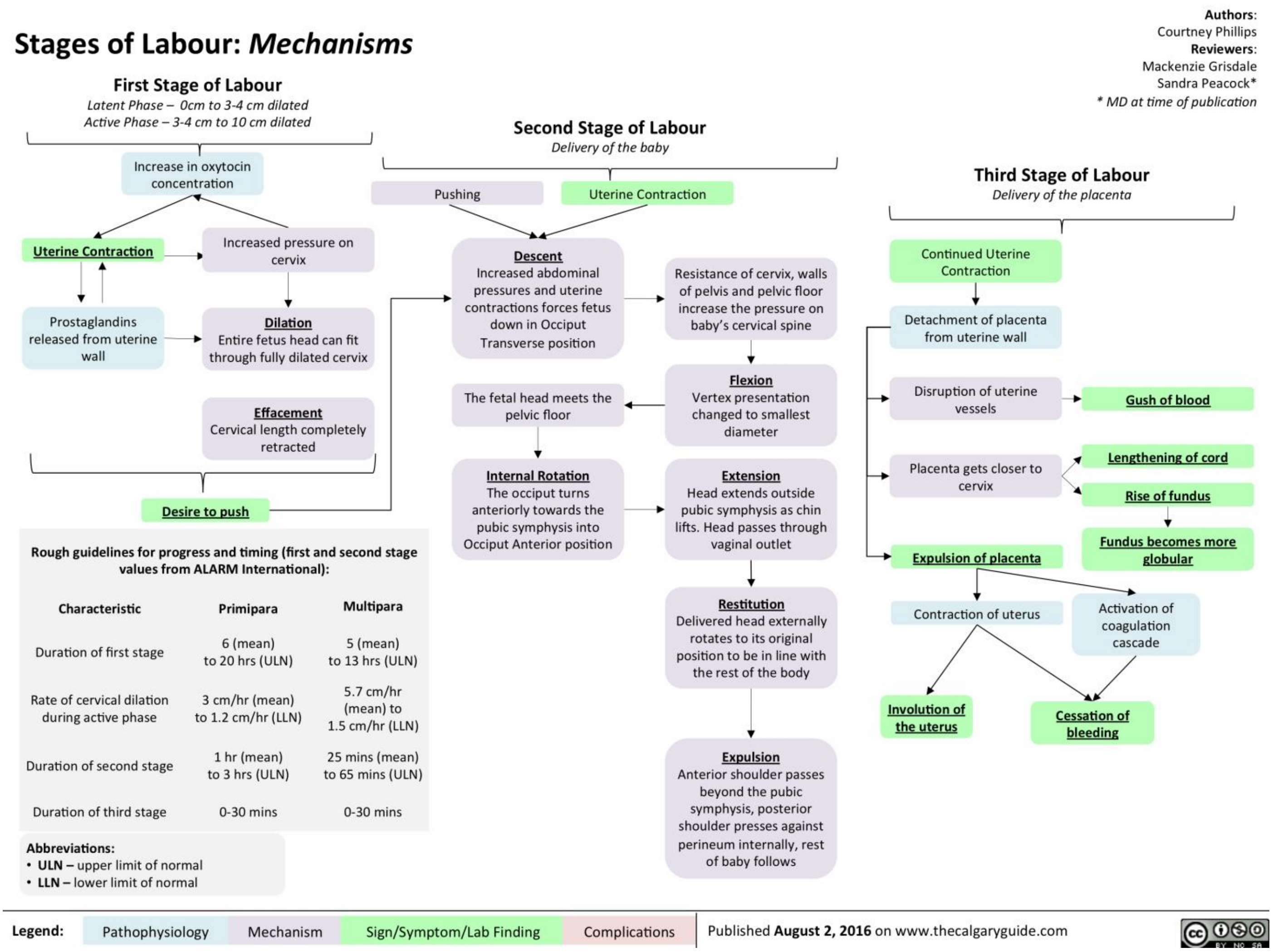

Stages of Labour: *Mechanisms*

Authors:
Courtney Phillips
Reviewers:
Mackenzie Grisdale
Sandra Peacock*
** MD at time of publication*

First Stage of Labour

Latent Phase – 0cm to 3-4 cm dilated
Active Phase – 3-4 cm to 10 cm dilated

Increase in oxytocin concentration

Uniterine Contraction

Increased pressure on cervix

Prostaglandins released from uterine wall

Dilation Entire fetus head can fit through fully dilated cervix

Effacement Cervical length completely retracted

Desire to push

Second Stage of Labour

Delivery of the baby

Pushing

Uterine Contraction

Descent Increased abdominal pressures and uterine contractions forces fetus down in Occiput Transverse position

Resistance of cervix, walls of pelvis and pelvic floor increase the pressure on baby's cervical spine

Flexion Vertex presentation changed to smallest diameter

The fetal head meets the pelvic floor

Internal Rotation The occiput turns anteriorly towards the pubic symphysis into Occiput Anterior position

Extension Head extends outside pubic symphysis as chin lifts. Head passes through vaginal outlet

Restitution Delivered head externally rotates to its original position to be in line with the rest of the body

Expulsion Anterior shoulder passes beyond the pubic symphysis, posterior shoulder presses against perineum internally, rest of baby follows

Third Stage of Labour

Delivery of the placenta

Continued Uterine Contraction

Detachment of placenta from uterine wall

Disruption of uterine vessels

Gush of blood

Placenta gets closer to cervix

Lengthening of cord

Rise of fundus

Fundus becomes more globular

Expulsion of placenta

Contraction of uterus

Activation of coagulation cascade

Involution of the uterus

Cessation of bleeding

Rough guidelines for progress and timing (first and second stage values from ALARM International):

Characteristic	Primipara	Multipara
Duration of first stage	6 (mean) to 20 hrs (ULN)	5 (mean) to 13 hrs (ULN)
Rate of cervical dilation during active phase	3 cm/hr (mean) to 1.2 cm/hr (LLN)	5.7 cm/hr (mean) to 1.5 cm/hr (LLN)
Duration of second stage	1 hr (mean) to 3 hrs (ULN)	25 mins (mean) to 65 mins (ULN)
Duration of third stage	0-30 mins	0-30 mins

Abbreviations:
- **ULN –** upper limit of normal
- **LLN –** lower limit of normal

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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Normal labour occurs in three stages, the length of which varies between women. By the time of delivery, the upper uterus is thick and muscular while the lower uterus is thin and more fibrous. This is the site of incision should a C-section be needed.

The initiation of labour is a natural process and the induction isn't entirely clear. Hormones that are particularly important include oestrogen, adrenaline, endorphins etc. Foetal and maternal ACTH is also increased, resulting in increased cortisol. Oxytocin also plays a role in uterine contraction. There is a significant increase in oxytocin receptors on the myometrium by this stage.

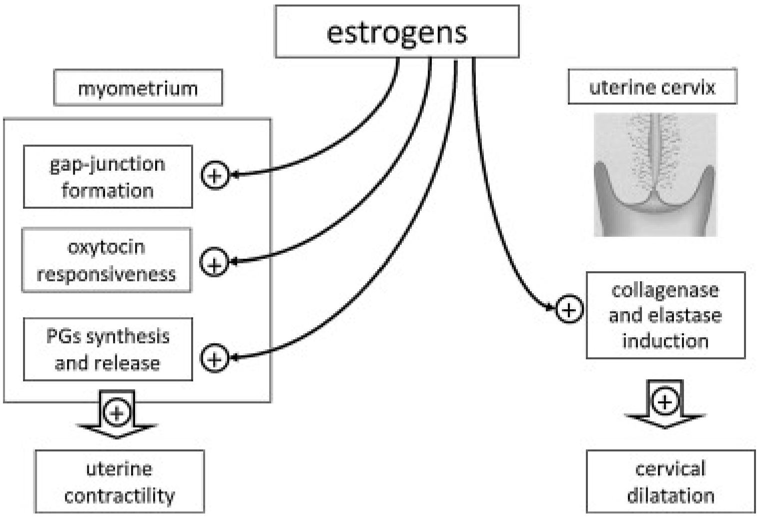
- Oxytocin initiates the timed uterine contractions and stimulates prostaglandin release
- Progesterone regulates gap junction between smooth muscle
    - Usually prohibits uterine contraction and prostaglandin release
- Oestrogen antagonises the effects of progesterone
    - Important to allow for contraction

Stage 1: ~14 hours

- Coordinated contractions begin
    - They occur every 2-3 minutes and occur between 5 and 10 minutes apart
- The mucus plug may be expelled resulting in a 'bloody show'
- Spontaneous rupturing of the waters may occur
    - This involves the rupture of the amniotic sac
- Cervical effacement and dilation begin and reaches 10cm
    - Effacement: the cervix is pulled up and thinned, usually becoming continuous with the lower uterine segment

Stage 2: 20 minutes - 2 hours

- This stage lasts from 10cm dilation through to delivery of the child
    - This is usually shorter for previous mothers and longer for first time mothers
- Contractions are more intense and occur more frequently
    - The mother often feels a serious desire and urge to begin pushing at this stage
- The baby's head should be rotated to face the back
    - Persistent posterior position is higher risk and labour pains are different and more painful
- Engagement of the foetus occurs when the widest diameter of the head has passed the pelvic inlet
- The amniotic sac can be broken by the doctor at this stage if it hasn't already been



- The baby's head will crown and adjust to the size of the opening
- After delivery of the head, the delivery of the rest of the baby should be relatively easy
    - One shoulder is delivered at a time
- The umbilical cord is cut

Stage 3: 60 minutes

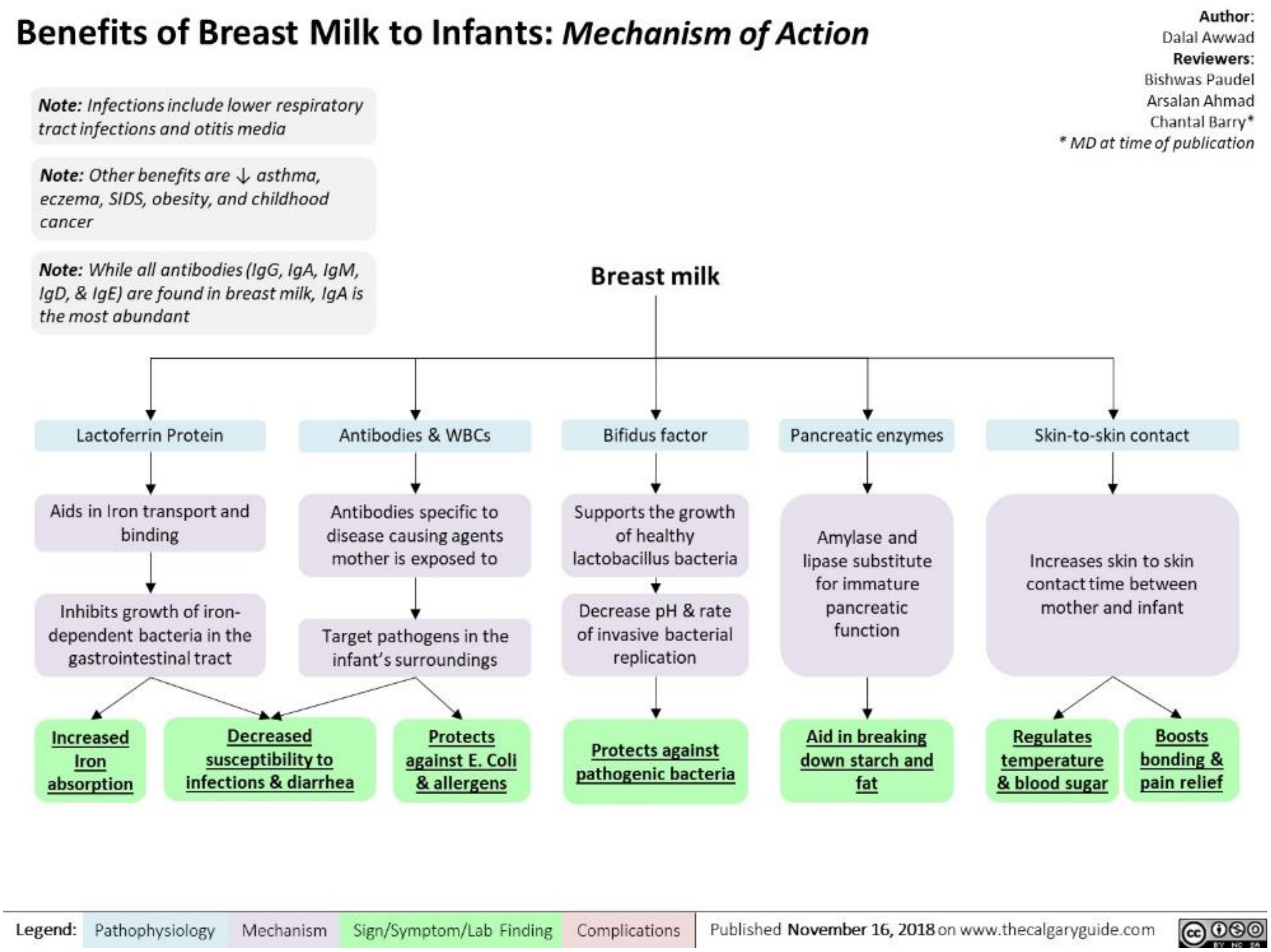
- Delivery of the afterbirth (placenta)
    - Indicated by loss of blood via the vagina, firming of the uterus and lengthening of the umbilical cord
- There are mild contractions that force the placenta out of the mother
    - This can be assisted with gentle traction on the umbilical cord

During labour the baby's wellbeing is routinely monitored using doppler ultrasound every 15 minutes in S1 and after every contraction in S2. This measurement can be escalated in a high-risk pregnancy, but this increases the risk of stressful false positives. The colour and volume of the amniotic fluid is also monitored.

The puerperium is the period from the completion of labour's 3rd stage to the return of the body to pre-pregnancy physiology. Usually this takes around 6 weeks and involves the commencement of lactation, reversal of the anatomical and physiological aspects of pregnancy and involution of the uterus.

Usually amenorrhoea occurs postpartum because of low oestrogen levels. This occurs because prolactin inhibits normal ovarian function. Ovulation can usually begin recurring after ~10 weeks.

BREASTFEEDING


Benefits of Breast Milk to Infants: Mechanism of Action
Author: Dalal Awwad
Reviewers: Bishwas Paudel, Arsalan Ahmad, Chantal Barry*
* MD at time of publication
Note: Infections include lower respiratory tract infections and otitis media
Note: Other benefits are ↓ asthma, eczema, SIDS, obesity, and childhood cancer
Note: While all antibodies (IgG, IgA, IgM, IgD, & IgE) are found in breast milk, IgA is the most abundant
Breast milk
Lactoferrin Protein
Antibodies & WBCs
Bifidus factor
Pancreatic enzymes
Skin-to-skin contact
Aids in Iron transport and binding
Inhibits growth of iron-dependent bacteria in the gastrointestinal tract
Antibodies specific to disease causing agents mother is exposed to
Target pathogens in the infant's surroundings
Supports the growth of healthy lactobacillus bacteria
Decrease pH & rate of invasive bacterial replication
Amylase and lipase substitute for immature pancreatic function
Increases skin to skin contact time between mother and infant
Increased Iron absorption
Decreased susceptibility to infections & diarrhea
Protects against E. Coli & allergens
Protects against pathogenic bacteria
Aid in breaking down starch and fat
Regulates temperature & blood sugar
Boosts bonding & pain relief
Legend: Pathophysiology Mechanism Sign/Symptom/Lab Finding Complications
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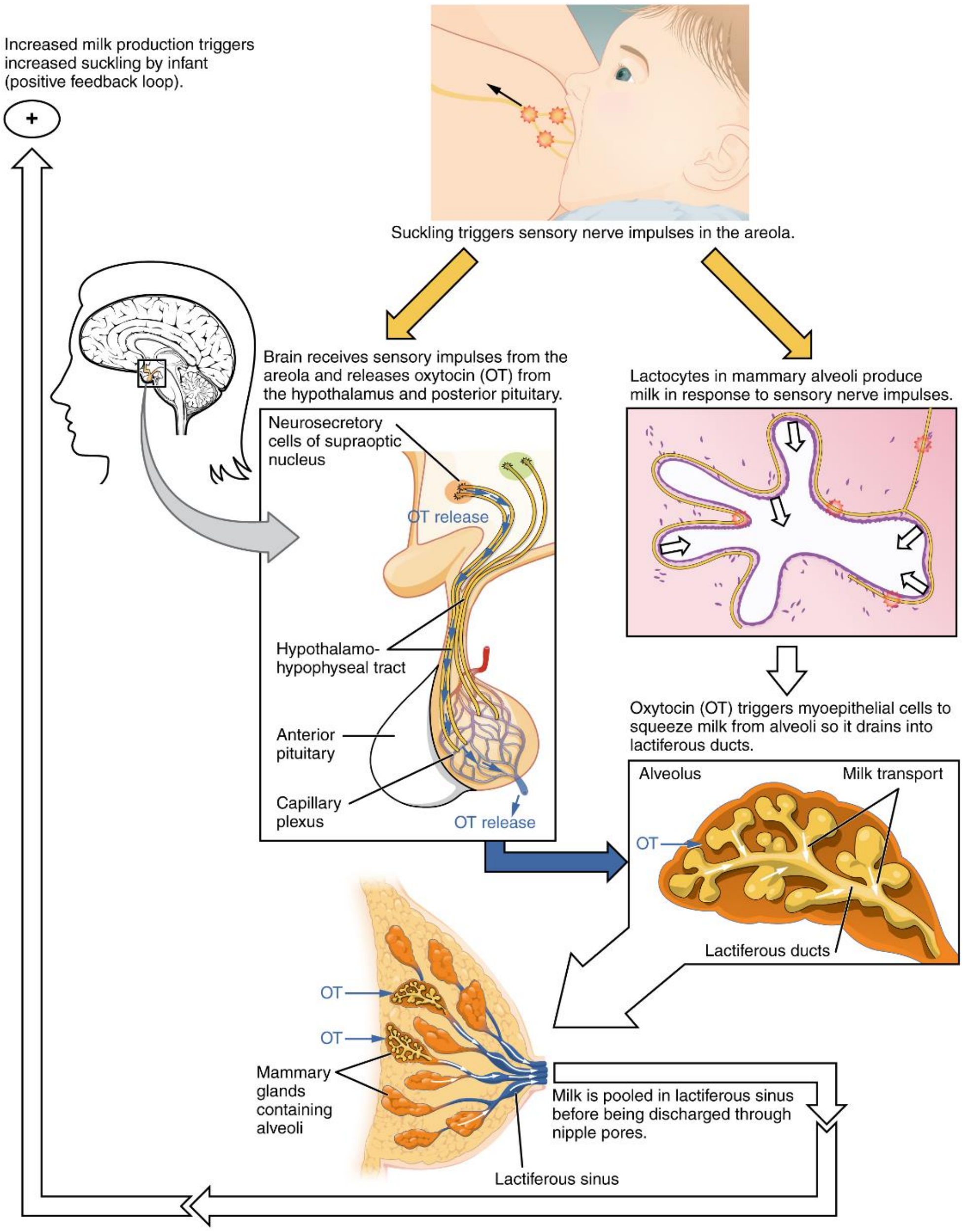
At puberty, there is a substantial amount of breast development under the influence of oestrogen. However, it is not until pregnancy occurs that the breasts undergo the structural and physiological changes required to produce milk. Milk production during pregnancy occurs in three stages:

- Lactogenesis I occurs during the development of the foetus under endocrine control
    - Placental lactogen, oestrogen and progesterone are all involved in promoting growth and development
    - There is decreased GnRH secretion and increased PRL levels
        - PRL acts on the breast tissue but steroid hormones block milk production from occurring
        - During this phase there may be some release of colostrum

            - This has a different composition to normal breast milk
- Lactogenesis II occurs after delivery of the baby
    - Decreased steroid hormone levels and the suckling action of the baby result in the release of milk
        - Oxytocin is produced in response to the suckling action of the baby
            - This is a peristaltic motion that requires a large amount of the breast (rather than just the nipple) to be engaged in the baby's mouth
    - Steroid hormone levels fall after delivery of the placenta which removes the suppression of milk production
    - Ideally breastfeeding should begin 30-40 minutes post delivery
        - It can be difficult to coordinate this for the first few days after delivery
- Lactogenesis III refers to the maintenance of milk production throughout the breast-feeding time of the child
    - The demand of the baby (i.e. the amount of suckling inducing milk let down) will often control the amount of milk produced
        - Frequent and on-demand feeding of the baby is ideal to ensure adequate milk production


Increased milk production triggers increased suckling by infant (positive feedback loop).
+
Suckling triggers sensory nerve impulses in the areola.
Brain receives sensory impulses from the areola and releases oxytocin (OT) from the hypothalamus and posterior pituitary.
Neurosecretory cells of supraoptic nucleus
OT release
Hypothalamo-hypophyseal tract
Anterior pituitary
Capillary plexus
OT release
Lactocytes in mammary alveoli produce milk in response to sensory nerve impulses.
Oxytocin (OT) triggers myoepithelial cells to squeeze milk from alveoli so it drains into lactiferous ducts.
Alveolus
Milk transport
OT
Lactiferous ducts
OT
OT
Mammary glands containing alveoli
Milk is pooled in lactiferous sinus before being discharged through nipple pores.
Lactiferous sinus

Breast milk is a largely water-based substance containing sugars, some fats, biologically active compounds and micronutrients. The composition of foremilk (milk expressed at the beginning of a feed) versus hindmilk (milk expressed at the end of a feed) is often different, with the later milk being more nutritionally dense, highlighting the need for long feeds. Key components of breast milk include:

- Milk lipids
- Carbohydrates
- Salts
- Ions
- Proteins (largely whey, casein etc)
- Micronutrients (ADEK, B and C, Fe, Ca, Zn etc)
- Some fats
    - The type of fat contained in the milk will depend on the maternal diet, but the amount contained within the milk is the same regardless of diet
- Bioactive substances: antimicrobial substances, immunoglobulins, miRNA, microbiome constituents, etc.

Breastfeeding can be difficult for some mothers and they may fear they are not providing their baby with adequate nutrition. The frequency of a baby feeding, a baby not being settled, and a slowing of growth after three months are all usually considered normal and not a cause for concern. Causes for concern include a lack of baby gaining weight, the infant's weight at two weeks being less than that at birth, reduced urine output, hard dry or green stools, lethargy or sleepiness in the baby or dehydration of the baby. These are signs of poor nutrition. This can be caused by:

- Poor milk production
    - Can be caused by a lack of stimulation
- Poor milk let down:
    - Can be physiological, due to drugs and/or smoking, or psychological factors (stress etc.)
- Inverted nipples making feeding difficult
- Breast reduction or insufficient breast tissue
- Poor infant intake
    - Can be caused by mechanical factors (i.e. cleft palate) as well as poor suck or infrequent feedings
- Low infant absorption
    - Vomiting, diarrhoea, malabsorption are all causes of this
- High infant energy needs
    - Can be due to congenital malformation (i.e. CHD), prematurely born baby etc.

Complications of poor or inadequate feeding include:

- Engorgement of the breast tissue
    - This occurs because supply is greater than demand resulting in milk stasis and oedema
        - This is a complication because it can impact baby attachment and exacerbate poor feeding

- Nipple trauma due to poor attachment

Contraindications to breastfeeding include:

- The use of some illicit drugs or medication
- Active TB or HIV infections
- Chemotherapy and radiation therapy

The benefits of breastfeeding include:

- It provides the optimal infant nutrition
- Shown to reduce further GI morbidity, otitis media occurrence, LRTI risk and acute illness
- Oxytocin released during suckling also contributes to involution of the uterus after delivery

DEVELOPMENT OF THE CHILD

Growth and development of the child can be broadly broken down into four categories:

- Physical growth:
  - Height
  - Length
  - Weight
  - Upper:lower body ratios
  - Arm span
  - Head circumference
- Cognitive development
  - Head circumference
  - Developmental milestones
  - Progression in school
- Pubertal development
  - Rapid growth in puberty
  - Changes in appearance (facial/pubic hair, secondary sex characteristics)
  - Cognitive changes due to frontal cortex changes
- Organ system-specific

Physical growth is considered important because it is often thought of as a proxy for health, disease, nutrition and development of a child. Growth failure in early life has the potential to have lasting and irreversible effects and the issues are easily identifiable, however birth weight does not predict future growth. Growth is plotted using a growth chart. Specific growth charts are available for disease groups as well as for the wider population. In addition to these charts, Tanner staging can be used to assess pubertal development, but these are crude measures.

- Birth weight should double by 6 months
- Birth weight should triple by 12 months

Developmental milestones:

- 1 month:
  - Jerky arm movements
  - Bring hands to face
  - Prefer black and white high contrast patterns
  - Smile spontaneously
  - Prefer human face shapes
  - Focuses on objects closer to face
- 3 months:
  - Raise head when laying down
  - Open and shut hands
  - Bring hands to mouth
  - Smile at parent's voices
  - Enjoy playing
  - Babble and imitate sound
  - Follow moving objects
- 6 months:
  - Rolls over
  - Sit up unsupported
  - Reaching for objects
  - Full colour vision
  - Uses sounds to express pleasure or displeasure
  - Can distinguish emotions via tone
  - Responds to name
- 12 months:
  - Crawl, pull self to stand
  - Pincer grasp for fine motor skills
  - Respond to requests
  - Use objects correctly
  - Explores objects
  - Find hidden objects
  - Use simple gestures
- 2 years:
  - Walk alone
  - Kick a ball

    - Climb on and off furniture
    - Scribble
    - Recognise faces, people and body parts
    - Can say several words
    - Use 2-4 simple sentences
    - Can imitate others
    - Imaginary play

Developmental disability is a term that refers to a permanent cognitive and/or physical impairment that occurs between birth and 18 years of age. It results in decreased capacity for major life activities. Developmental disabilities can be categorised into"

- Global: affects all systems
- Motor:
    - Gross motor: i.e. running etc.
    - Fine motor: hand and finger movement etc.
- Personal/Social
- Language
    - Expressive: spoken language
    - Receptive: understanding language
        - Usually a disability in receptive language is a more difficult disability and a larger warning sign that developmental disability in expressive language
    - Pragmatic

Developmental disability can also be categorised as a delay (the development is not occurring at the required rate but is constant) or regression (the loss of previously learned behaviours or skills). Regression of previously learned skills is a larger red flag than a delay. Typically, the developmental delay gap will widen over time rather than allowing the child to 'catch up'

Presentations of developmental disability are highly varied and dependant on the affected systems. These may include:

- Behavioural issues or disturbances
- Sleep disturbances
- Seizures
- Dysmorphism
- Neurocutaneous stigmata

Psychological development of the child begins at birth and continues through the adulthood. The two psychological developmental categories are cognitive and socioemotional.

Infancy: 0-2 years

- Cognitive
    - Language acquisition
        - Receptive language (understanding of language) develops in advance of expressive language (ability to talk)
    - Object permanence
- Socioemotional:
    - Emotional expression
    - Emotional self-regulation:
        - Soothing becomes internalised
        - Distraction
        - Temperament development
    - Attachment to caregivers
- Key theories of infancy include the Bowlby attachment theory which states that attachment is important to survival. The parents provide a safe base from which the child can explore and learn about the world. This can be seen in the child's responses of fear during times when parents are absent and relief when they return. This response is often exacerbated in foreign environments such as hospitals.
    - Insecure attachment can be seen when children become extremely and disproportionately distressed or not distressed at all when the child leaves

Early childhood: 2-5 years

- Cognitive:
    - Growing vocabulary
    - Dramatic play
    - Theory of mind: the development of the idea that what one person knows can be different from what others know
- Socioemotional:
    - Social display rules: understanding what is and isn't okay
        - This often develops later in children from disadvantaged backgrounds
    - Development of preferred playmates
    - Gender role and racial awareness
- Key theories include Piaget's pre-operational stage and Erikson's initiative vs guilt. Piaget states that this stage involves the use of language and symbolic representation along with an egocentric view of the world. Erikson's theory states that the child is testing the limits of self-assertion and purpose.

Middle Childhood: 6-12 years

- Cognitive:
    - Problem solving capacity
    - Attention developments
    - Short term and long-term memory develops
    - Reading and writing capacity increases
- Socioemotional:

    - Develops a sense of self and place
    - Sense of achievement is possible
    - Peer friendships develop
        - This is particularly important for children and they worry about how they are perceived by other people, age segregation of friendships becomes common and so does gender and ethnic segregation
- Key theories include Erikson's industry vs inferiority and Vygotsky's theory. Erikson states that during this period the child is developing mastery, focus, competence and productivity. Vygotsky states that the environment in this stage plays an important role: the zone of proximal development refers to the gap from what the child can do independently compared to what the child can do with support.

Adolescence: 12-18 years

- Cognitive:
    - Abstract thought develops
    - Development of adult interests
- Socioemotional:
    - Interest in sexual relationships
    - Dating and first jobs
    - Peaks in risk taking behaviour
    - Peak in mental health problems
        - Sharply increases at 12 years old. This is likely because the time of physical transition, emotional maturation and vulnerability to stressful life events. There is an emphasis of interpersonal relationships and hormone fluctuations occurring simultaneously.
        - Mental health assessments in adolescence are important to assess risk and monitor progression: some onsets may be indicative of further development in later life and early intervention can help prevent these.
- Key theories include Piaget who states that this is the age of formal operation as the child can conduct mental manipulation based on thoughts rather than observable things and Erikson's theory that this stage involves identity vs confusion wherein the child develops a strong sense of self amidst feeling confused and insecure.

Adulthood:

- Cognitive:
    - Development of post-formal thought
    - Expertise and practical intelligence
    - Achievement of wisdom
- Socioemotional:
    - Finding a mate, making a home
    - Family changes
    - Earning a living and development of a career

Deviation in normal psychological development can occur similarly to physical development: in a delayed or regressive pattern.

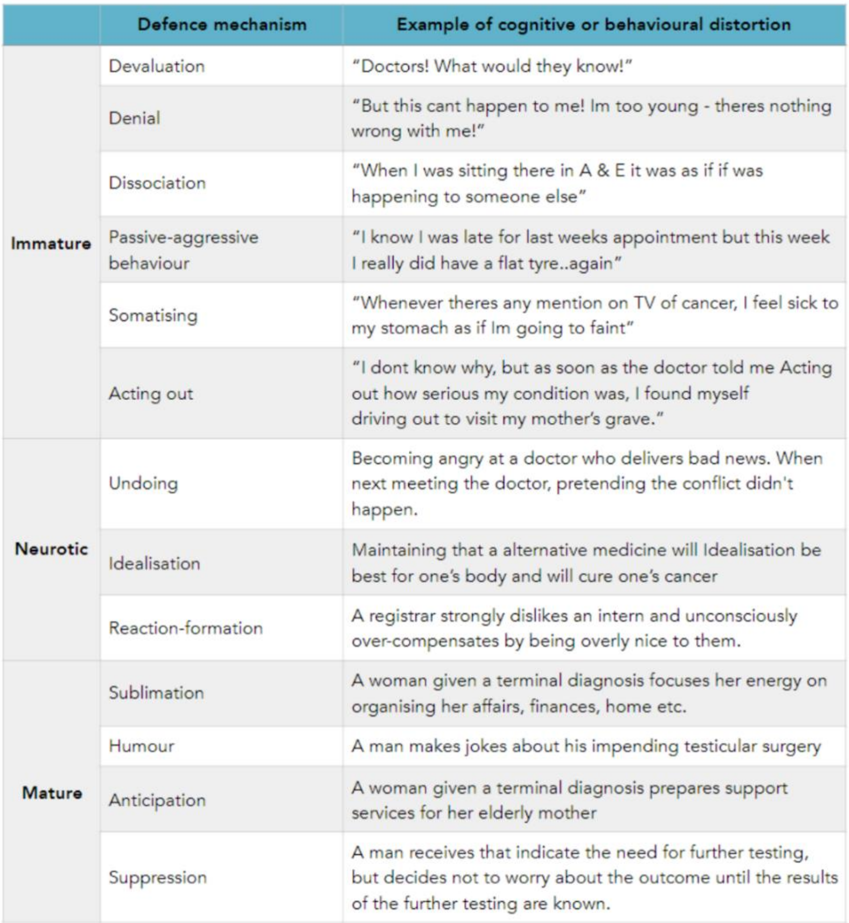
Coping mechanisms include conscious and deliberate strategies to deal with environmental stressors that develop with psychological maturity. They can be both adaptive and maladaptive.

- Trait coping refers to the way people cope with stress in everyday life
- State coping refers to the ways people copy with stress in specifically stressful situation

Coping capacity and mechanisms can be assessed using the COPE questionnaire. Coping mechanisms include both adaptive and maladaptive mechanisms; adaptive are those that improve stress and maladaptive are those that increase stress. This is measured via salivary cortisol. They include:

- Positive action
    - Self-distraction
    - Active coping
    - Instrument support
- Social support
    - Emotional support
    - Humour
    - Religion
- Cognitive shaping
    - Positive reframing
    - Planning
    - Acceptance
- Maladaptive:
    - Behavioural disengagement
    - Venting
    - Denial
    - Substance use
    - Self-blame

Defence mechanisms include the mechanisms employed against incompatible ideas or emotions in order to preserve imagery and stability of self. This can involve self-deception and a distortion of



	Defence mechanism	Example of cognitive or behavioural distortion
Immature	Devaluation	"Doctors! What would they know!"
	Denial	"But this cant happen to me! Im too young - theres nothing wrong with me!"
	Dissociation	"When I was sitting there in A & E it was as if if was happening to someone else"
	Passive-aggressive behaviour	"I know I was late for last weeks appointment but this week I really did have a flat tyre..again"
	Somatising	"Whenever theres any mention on TV of cancer, I feel sick to my stomach as if Im going to faint"
	Acting out	"I dont know why, but as soon as the doctor told me Acting out how serious my condition was, I found myself driving out to visit my mother's grave."
Neurotic	Undoing	Becoming angry at a doctor who delivers bad news. When next meeting the doctor, pretending the conflict didn't happen.
	Idealisation	Maintaining that a alternative medicine will Idealisation be best for one's body and will cure one's cancer
	Reaction-formation	A registrar strongly dislikes an intern and unconsciously over-compensates by being overly nice to them.
Mature	Sublimation	A woman given a terminal diagnosis focuses her energy on organising her affairs, finances, home etc.
	Humour	A man makes jokes about his impending testicular surgery
	Anticipation	A woman given a terminal diagnosis prepares support services for her elderly mother
	Suppression	A man receives that indicate the need for further testing, but decides not to worry about the outcome until the results of the further testing are known.

accurate perception of reality. The use of immature defence mechanisms can result in negative adult adjustment and occurrence of pathology. Defence mechanism employment maturity increases and improves with age. Tendencies of stress responses include:

- Adult males: hyperarousal
- Young children: dissociation
- Females: social affiliation

PUBERTY

Puberty is defined as the developmental phase between childhood and adulthood in which functional maturation of the reproductive organs and external genitalia occurs. Puberty occurs in males and females at different ages. The average is 1-2 years earlier for male pubertal onset.

- Generally occurs in males between 9-13.5
  - Precocious puberty occurs in children under 9
  - Delayed puberty occurs over 14 years
- Generally occurs in females between 8 -14 (there is significant variation in onset for females)
  - Precocious puberty occurs <8
  - Delayed puberty can be defined as:
    - Absence of breast development by 13
    - Absence of menarche by 16

Puberty is largely driven by GH, IGF-1 and the sex hormones. Prior to puberty there is a low-amplitude secretion of LH and FSH secretion and low sex steroid secretion. Oestradiol is usually still higher in pre-pubertal girls than boys because of the basal ovarian activity but there are equal levels of sex hormone binding globulin.

- GnRH secretion increases in amplitude and frequency, particularly in the early morning
  - This results in an increase in sex steroid levels
  - The signal for this to occur is not entirely clear; kisspeptin signalling is likely involved
- The gonadotrophins become less sensitive to negative feedback inhibition
- Oestrogen is very important in puberty as it is responsible for the closure of epiphyseal plates which causes a cessation of growth
  - This is one of the reasons women are generally shorter than men: they have higher levels of oestrogen earlier, and thus stop growing earlier.
- The general health status of the individual is also important: factors such as nutritional status, genetics and the social environment are all important.

Female puberty occurs in the following stages:

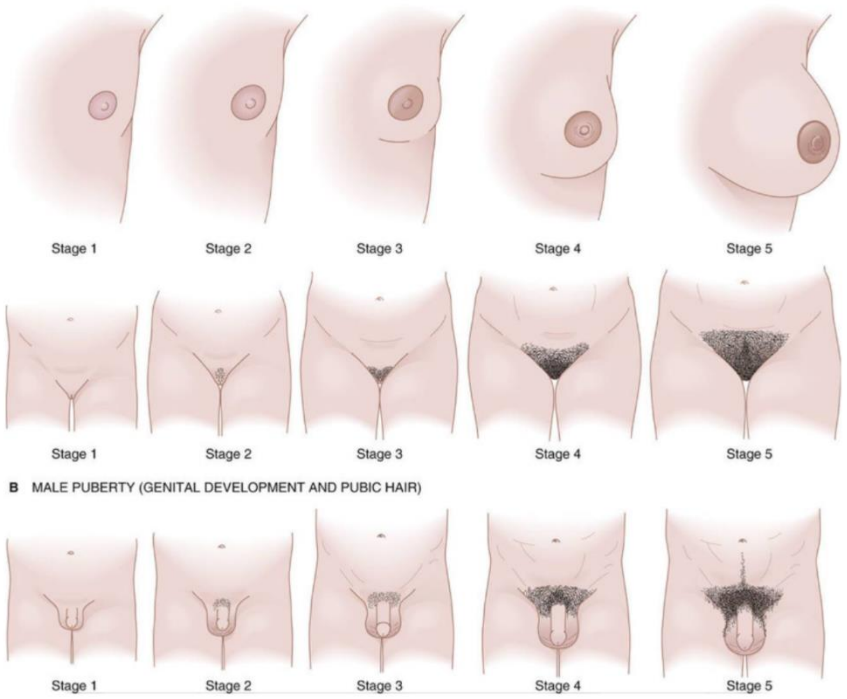
- Adrenarche occurs
- Gonadarche occurs
- Thelarche occurs
  - This usually happens between 8-11 years
  - This occurs because of oestrogen
    - While the final stages are determined by genetics and nutrition the developmental stages are similar in all people
- The growth spurt occurs
  - This is usually less pronounced in females compared to males
- Pubarche occurs
  - This occurs in response to adrenal androgen
  - Vaginal development occurs around the same time
    - This includes the enlargement of the labia minora and majora, the dulling of the vaginal mucosa and a white vaginal secretion prior to menarche
  - This occurs around the same time as the uterine and ovarian development
    - Prolonged oestrogen stimulation causes an elongation of the uterus resulting in an increased fundus to cervix ratio
    - Prolonged oestrogen stimulation causes an enlargement of the ovaries and a transition from a small cystic appearance to a multi-cystic appearance
- Menarche occurs
  - Average age of onset is 13 years
  - Ovulation occurs only if the correct oestrogen positive feedback occurs in the mid cycle resulting in the LH surge
    - 90% of the menstrual cycles in the first-year post-menarche are anovulatory
    - Many of the initial menstrual cycles are irregular

Male puberty occurs in the following stages:

- Adrenarche occurs
- Gonadarche occurs
  - Enlargement of the testes generally occurs because of FSH stimulation causing the growth of the seminiferous tubules
  - LH stimulation also causes the development of the Leydig cells
  - Penile enlargement usually follows this
- Pubarche occurs
  - This does not necessary occur in sync with the maturation of the gonads
  - The initial development of pubic hair occurs in response to adrenal androgens
- Spermarche occurs
- Growth spurt occurs
- Androgenic hair growth occurs
  - This is a response to adrenal androgens and involves the male-pattern hair growth outside of the pubic hair

In males the first visible sign of puberty is the enlargement of the testicles, while in females it is the development of the breasts.

The Tanner Stages are the key measure used at assess pubertal growth and development. They are broken into the categories of pubic hair, breast development and genital development.



- Pubic hair:
    - Stage 1: No hair or soft hair grows over the pubis
    - Stage 2: Sparse and pigmented hair becomes slightly curled and grows mainly on the labia or penile base
    - Stage 3: Hair is darker, coarser and curlier and spreads over the pubic symphysis
    - Stage 4: Adult pubic hair but does not extend to the inner thighs
    - Stage 5: Adult pubic hair extends to the inner thighs
    - Stage 6: Growth of pubic hair along the linear alba (largely in males)
- Breast development:
    - Stage 1: prepubertal appearance and size (elevation of the nipple is possible)
    - Stage 2: Mammary glands enlarge to form a breast bud; the nipple protrudes and the areolar diameter increases
    - Stage 3: Mammary glands enlarge, and the breast bud increases beyond the areola
    - Stage 4: Nipple and areola form a secondary mount which project above breast tissue
    - Stage 5: Adult breast; the papilla projects and the areola doesn't
- Genital development:
    - Stage 1: Prepubertal appearance and size of the testes, scrotum and penis
    - Stage 2: Testicular volume increases, no increase in penile size, scrotal skin darkens and texture changes
    - Stage 3: Enlargement of the testes and scrotum continues, penis lengthens
    - Stage 4: Testicular volume increases, scrotum grows and the penis length and with increases
    - Stage 5: Testes, scrotum and penis attain adult appearance and proportion

The key morphological changes that occur during puberty include:

- Growth spurts:
    - Increased growth in the trunk and limbs
    - Assessed using growth velocity charts
    - Variation between the sexes
        - Occurs around two years earlier for girls
    - Lasts for around 2 years on average
- Bone growth:
    - Accelerated during puberty
    - Increased mineralisation and density
- Body weight and composition changes:
    - Males body fat decreases and lean body mass increases
    - Females have a gradual increase in body fat
- Skin changes:
    - Pubertal hormone levels increase sebum secretion and cause excessive sweating
    - This can result in acne, hyperhidrosis and hair issues

NUTRITION DURING PREGNANCY

The general guidelines for pregnancy include:

- Eating the recommended number of serves of the food groups throughout pregnancy and breastfeeding
- Consuming small to moderate amounts of caffeine
- No alcohol
- No illicit substances
- Taking iodine supplements of 150 micrograms
- Taking a folic acid supplement
    - These should ideally be commended 12 weeks prior to conception
    - Individuals who have had previous pregnancies with NTD are recommended to take higher dose supplements
- Iron supplements are indicated in the event of deficiency
- Vitamin D supplements are indicated in deficiency
- Increase fluid intake

Weight during pregnancy can be difficult to discuss. It is normal to gain weight during pregnancy and any kind of weight loss diets are not recommended. Being in the healthy weight range prior to pregnancy increases fertility for both men and women. During pregnancy, weight is important as both underweight and overweight mothers are at increased risk of complications.

- Underweight mothers are more likely to have low birth weight infants
- Overweight mothers are more likely to experience pre-eclampsia, gestational diabetes, high birth weight babies etc.

The amount of weight gain is dependent on the pre-conception BMI.

- Women underweight: gain 12.5-18kg
- Women of normal weight: gain 11.5-16kg
- Women overweight: gain 7-11.5kg
- Women of obese weight: gain 5-9kg

The additional energy requirements during pregnancy are equivalent to a sandwich and piece of fruit per day.

The macronutrient requirements for pregnancy increase slightly.

- Protein recommendations: 21g/day
  - Deficiency can cause reduced foetal growth and low birth weight
  - Deficiency is linked to increased perinatal mortality
- Fatty acid requirements (particularly omega 3 and 6) are important and recommendations are around 500mg
  - Deficiency is rare but can contribute to low birth weight and early delivery
- Carbohydrate requirements increase
  - Ketogenic diets are not recommended
    - The effect of ketones on the placenta and baby have not been studies
    - Low card diets can cause the loss of fluid

Micronutrient requirements sometimes increase during pregnancy

- Calcium requirements do not increase in pregnancy
  - Maternal adjustments include decrease urinary losses and increase gastrointestinal absorption
- Iron requirements increase slightly due to the production of foetal blood and increased blood volume in pregnancy
  - Deficiency causes intra-uterine growth restriction, low birth weight etc.
  - Anaemia during pregnancy can contribute to reduced oxygen delivery to the foetus
  - Iron absorption in the gut is not sufficient to compensate for increased requirements during pregnancy; the stored iron in the body is the primary source of extra iron during pregnancy
- Folate and iodine requirements increase during pregnancy and supplementation is recommended
- Vitamin b12 supplementation is sometimes required (particularly for vegans)
  - B12 deficiency is associated with infertility
- Vitamin A is important for many systems and development, but supplementation is not recommended
  - Excess vitamin A can be toxic

Food safety is important during pregnancy because of the potentially harmful effects of illness during pregnancy. Key concerns include:

- Listeria: this infection can lead to miscarriage, stillbirth, premature birth or illness in the baby
  - Usually listeria is contracted from processed deli meats, soft cheeses, pre-cut fruits or salads etc.
- Salmonella should be avoided
  - This includes raw or partially cooked eggs
- Toxoplasmosis is risky for the baby (TORCH organism)
  - Found in raw or undercooked meats
  - Cat litter exposure increases risk

Many women may be concerned about the development of allergies in their child due to exposure in early life. There is no evidence to support this claim. The general recommendations include breastfeeding for up to 6 months alongside the introduction of a variety of solids around 4-6 months.

- Giving children common food allergens in the early stages is safe
- Cow's milk is not recommended for infants <12 months

AGING AND MENOPAUSE

PHYSIOLOGY OF AGING

Physiological changes are normal during menopause.

Renal changes include:

- Reduced renal mass
  - Causes reduced renal blood flow
  - eGFR drops by 8mL/min/decade on average
- Increased glomerulosclerosis
- Results in increased blood pressure
- Changes to renal excretion of drugs meaning dose alterations are required
  - This increases the risk of ischemic or toxic damage
- Increased risk of renal failure
- Lower levels of creatinine are normal due to a decreased muscle mass

Changes to body fluid balance:

- Impaired sodium and water conservation
- Delayed less thirst response
- Increased ADH concentration and secretion response to decreased baroreceptors
  - Loss of renal responsiveness
  - Loss of diurnal ADH secretion
- Total body water decreases caused by increased fat and less muscle
- Ability to concentrate urine decreases due to renal changes

    - Causes vulnerability to dehydration and increased likelihood for the development of pre-renal failure
- Increased nocturia causes decreased sleep and decreased quality of life
- More likely to develop hyponatraemia due to salt-losing nephropathy
- Delayed response to fluid changes

Gastrointestinal and hepatic changes:

- Swallowing presbyphagia: the loss of coordination between action contraction in involuntary oesophageal sphincter relaxation
    - This increases susceptibility to aspiration pneumonia
- Loss of neural gut control causing a slowed transit time
    - Results in constipation
- Reduced hepatic blood flow
    - Can affect drug metabolism
- Reduced secretion of hydrochloric acid
    - This increases susceptibility to B12 and iron deficiency
    - Can affect the metabolism of some drugs

Respiratory changes:

- Reduced pulmonary capacity due to decreased body thorax elasticity, loss of muscle mass and weakening, decreases in surface area for gas exchange and a decrease in CNS responsiveness
    - Chronically low oxygen levels reduce tolerance to illness and impairs wound healing
    - Decreased exercise tolerance
- Loss of cilia
    - Increased risk of lung infections
- Loss of cough reflex
- Abnormal breathing patterns can cause sleep apnoea

Cardiovascular changes:

- Decreases in ability to raise heart rate, compliance of ventricles, catecholamine response, conduction pathway efficacy due to fibrosis, vasoconstriction capacity
    - Results in decreased cardiac output, increased peripheral resistance
    - Results in reduced end organ perfusion
    - Can cause arrythmias and heart murmurs

Nervous system changes:

- Neuron loss cannot be regenerated causing cerebral atrophy and a reduction in brain size
- Demyelination of peripheral nerves
    - Reduced reflex response
    - Minor loss of peripheral sensation
- Alteration to neurotransmitters and responses
    - Increases susceptibility to some drugs
- Increased periventricular white patter changes – increase in hypodense areas resulting in increased occurrence of non-specific old-age issues
- Parasympathetic outflow decreases and sympathetic tone increases
    - Decreased response to beta-adrenergic responses causes a reduction in the ability of aortic arch and carotid sinus to respond to baroreceptor signalling
    - Can result in postural and post-prandial hypotension

Musculoskeletal changes:

- Sarcopenia
- Osteoporosis
- Osteoarthritis

Immune changes:

- 90% involution of thymic function
- B and T cell functionality decline
- Reduced macrophage functionality
- Reduced cytokine response and regulation
- Increased levels of autoantibodies
- Results in the increased susceptibility to infections, reactivation of viral and bacterial infections, increased cancer susceptibility and autoimmune disease peaks

Skin:

- Skin degradation occurs due to atrophy, fibrosis and decreased cell turnover
- Decreased vitamin D production
- Thermoregulation decreased due to decreased skin fat levels

Endocrine:

- Testosterone and oestrogen levels decrease

Many aging individuals suffer from multiple chronic diseases which worsen one another. The impact of disease and aging on the elderly is dependent on their health and social status and risk factors.

The aged individuals often have atypical presentations of illness, including missing symptoms and signs. This makes diagnosis of conditions in the elderly more difficult. Many elderly people have had significant medical treatment and iatrogenic causes are important to consider, particularly when polypharmacy is involved. This means care for the elderly should be multi-disciplinary and outpatient focused as much as possible. Assessment should include medical, functional, cognitive, psychosocial factors as well as input from others in the patient's life.

- The term 'geriatric giants' refers to the range of non-specific presentations of the elderly in acute unwellness
    - Intellectual failure
    - Incontinence

  - Immobility
  - Instability and falls
  - Iatrogenic disease
  - Functional decline

Frailty in the aged occurs due to a decreased functional reserve and capacity to resist stressors. It is the result of cumulative decline across many physiological systems and increased adverse outcomes for the elderly. Key factors of frailty include a reduced appetite, malnutrition, reduced weakness and muscle tone, increased susceptibility to falls and reduced mobility. Frailty is often a complication of hospitalisation; functional decline and immobility complications occur more frequently and are difficult to recover from for the elderly.

- Immobility as a result of frailty (i.e. due to injuries etc) can cause pressure areas reduced muscle strength, constipation, DVT, osteoporosis, depression etc.
- Frailty can often be reversed or lessened with rehabilitation

MENOPAUSE

Menopause is defined as the permanent cessation of menstruation due to the loss of ovarian follicular activity. It usually occurs in women aged between 45-55 and is precluded by a period known as perimenopause wherein hormonal changes cause typical symptoms.

- Natural menopause occurs at the expected age
  - It is the result of the ovarian ova supply reaching 0 (usually after 300-400 ovarian cycles)
- Premature menopause occurs before 40
- Early menopause occurs before 45
  - When premature or early menopause occurs spontaneously these conditions can be referred to as primary ovarian insufficiency
  - Often these patients have more severe perimenopausal symptoms
- Induced menopause occurs as a result of radio or chemotherapy or due to the surgical removal of the ovaries

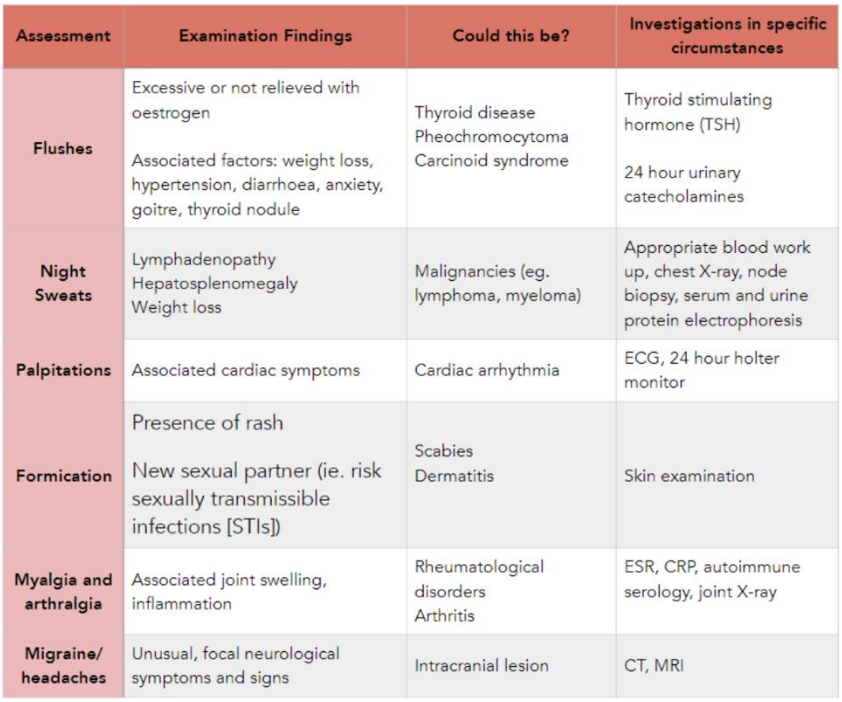
The Straw staging system is used to categorise the stages of female development from reproductive age through to post-menopause.

Tissue changes that occur during menopause include:

- Involution of the ovary, uterus and breasts
  - The breast duct and acini number decrease and the epithelial and myoepithelial cell size decreases while the breast stroma is gradually replaced by fibrous stroma
- Atrophy of the vulva and vagina
  - The introitus narrows and there is a loss of vaginal moisture alongside a pallor of the epithelium
- Reduction in bone density due to decreased oestrogen
  - This increases susceptibility to osteoporosis
- Increased atherogenicity due to changes in the lipid profile
- Decreased progesterone levels causes increased proliferation and disorganisation of the endometrial tissue resulting in heavy bleeding in perimenopause, followed by decreases in oestrogen declines resulting in atrophy of the endometrium
- Reduction in oestrogen causes an increase in blood pressure, LDL and triglyceride levels which predispose women to heart disease
  - This occurs because of the withdrawal of the positive effects of oestrogen on the intima of the arteries

Symptoms of perimenopause and menopause include:

- Vasomotor symptoms:
  - Hot flushes
  - Night sweats
  - Palpitations
  - Light-headedness
  - Migraines
- Urogenital symptoms
  - Atrophic vaginitis
  - Vaginal dryness
  - Dyspareunia
  - Libido decreases
  - Stress incontinence
- Musculoskeletal symptoms
  - Nonspecific muscular and joint aches and paints
- Skin changes
  - Dryness
  - Increased facial hair
  - Formication
- Psychological changes
  - Tiredness
  - Irritability
  - Depression, anxiety and tension
  - Poor memory and concentration
  - Sleep disturbances



Assessment	Examination Findings	Could this be?	Investigations in specific circumstances
Flushes	Excessive or not relieved with oestrogen Associated factors: weight loss, hypertension, diarrhoea, anxiety, goitre, thyroid nodule	Thyroid disease Pheochromocytoma Carcinoid syndrome	Thyroid stimulating hormone (TSH) 24 hour urinary catecholamines
Night Sweats	Lymphadenopathy Hepatosplenomegaly Weight loss	Malignancies (eg. lymphoma, myeloma)	Appropriate blood work up, chest X-ray, node biopsy, serum and urine protein electrophoresis
Palpitations	Associated cardiac symptoms	Cardiac arrhythmia	ECG, 24 hour holter monitor
Formication	Presence of rash New sexual partner (ie. risk sexually transmissible infections [STIs])	Scabies Dermatitis	Skin examination
Myalgia and arthralgia	Associated joint swelling, inflammation	Rheumatological disorders Arthritis	ESR, CRP, autoimmune serology, joint X-ray
Migraine/ headaches	Unusual, focal neurological symptoms and signs	Intracranial lesion	CT, MRI

The criteria for diagnosis of menopause includes the age of onset, the lack of periods for 12 months and the presence of menopausal symptoms. Laboratory criteria include an increased FSH level and a decreased oestrogen level. Lab tests are usually conducted only when there is doubt about the diagnosis.

Management of menopause includes lifestyle stages and complementary therapies. Prescription medicines can include:

- Alpha-adrenergic agonists
- Beta blockers
- SSRIs

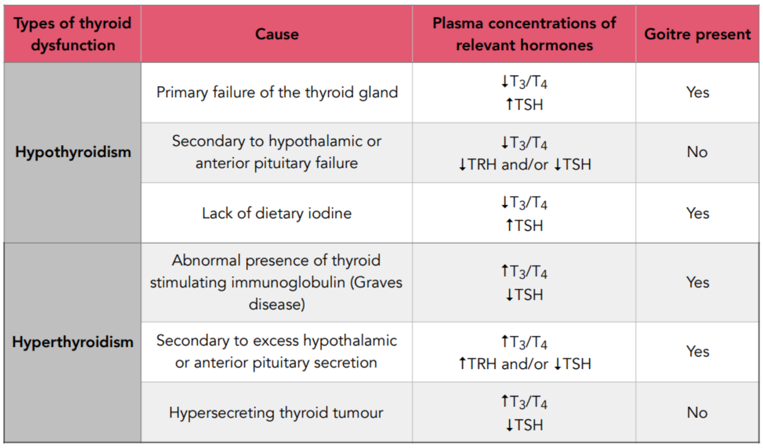
- Menopausal hormone therapy
  - This involves the replacement of oestrogen and progesterone to provide symptomatic relief and decrease risk of disease development
  - This can use used for as long as needed unless contraindicated
  - There are many types of MHT including oestrogen, progesterone, testosterone and various combinations.
    - Vaginal creams can be very useful in the treatment of urogenital symptoms
  - MHT increases the risk of:
    - Breast, endometrial and ovarian cancer
    - Thrombosis and stroke
    - Gallstones
    - Side effects such as nausea, bloating, breast enlargement, breakthrough bleeding and PMS symptoms
- Contraception should be continued for 1 year after menopause (in over 50) or 2 years (if under 50) if no conception is desired

THYROID AND PARATHYROID PATHOLOGY

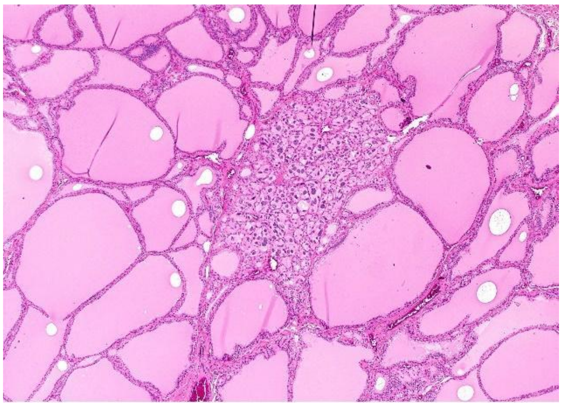
HYPERTHYROIDISM

Hyperthyroidism occurs when there is excess thyroid hormone produced. It leads to a number of classic signs and symptoms which include:

- Weight loss
- Tachycardia
- Palpitations and/or arrythmias
- Sweating
- Heat intolerance
- Irritability
- Fatigue
- Pretibial myxoedema
  - This occurs because of fibroblast activation by TSH antibodies in Grave's Disease resulting in glycosaminoglycan accumulation in the dermis
- Pigmented papules (in Grave's disease)
- Goitre
  - This can be both nodular (usually cysts or neoplasms) or diffuse (usually a disease) as well as benign and malignant.
  - May present with Pemberton's sign
  - May be a thyroid bruit due to overactive gland
- Hyperreflexia
- Eye signs:
  - Dry or gritty eyes
  - Double vision
  - Pain with movement or behind the eye
  - Lid lag
  - Lid retraction
  - Exophthalmos
  - Decreased visual acuity



Types of thyroid dysfunction	Cause	Plasma concentrations of relevant hormones	Goitre present
Hypothyroidism	Primary failure of the thyroid gland	↓T_3/T_4 ↑TSH	Yes
	Secondary to hypothalamic or anterior pituitary failure	↓T_3/T_4 ↓TRH and/or ↓TSH	No
	Lack of dietary iodine	↓T_3/T_4 ↑TSH	Yes
Hyperthyroidism	Abnormal presence of thyroid stimulating immunoglobulin (Graves disease)	↑T_3/T_4 ↓TSH	Yes
	Secondary to excess hypothalamic or anterior pituitary secretion	↑T_3/T_4 ↑TRH and/or ↓TSH	Yes
	Hypersecreting thyroid tumour	↑T_3/T_4 ↓TSH	No



Graves' disease (treated): small nodule of atypical cells with bizarre nuclei, this is a sign of anti-thyroid or radioiodine treatment (H&E, low power)

Hyperthyroidism is also sometimes referred to as thyrotoxicosis. This term refers to an excess of thyroid hormone and can be caused by all the pathological causes of hyperthyroidism as well as excess thyroxine treatment. Hyperthyroidism can be primary (an issue with an organ itself) as well as secondary (due to external causes).

Hyperthyroidism has many causes:

- Grave's Disease: This autoimmune disease occurs when the body produces antibodies that stimulate the thyroid gland to produce thyroid hormone by mimicking TSH.
  - Grave's disease causes a stimulation of the thyroid follicles resulting in proliferation and hyperplasticity of the cells. This is not an inflammatory disorder, however, so no white blood cells are present. On histology this appears as:
    - More than one layer of cell lining each follicle
    - Infolding of the thyroid follicle walls
    - Scalloping of the colloid within the follicle due to the increased uptake of colloid by cells
    - Grave's disease is diagnosed by thyroid hormone tests as well as elevated anti-TSH receptor antibodies
- Thyroiditis: this is a painful inflammation of the thyroid gland that can occur for a variety of reasons
  - Hashimoto's Thyroiditis
    - Gland destruction occurs due to autoimmune reactions resulting in an initial release of thyroid hormone that can sometimes cause initial hyperthyroid symptoms due to the release of thyroid hormone from damaged follicles
  - Lymphocytic thyroiditis
    - Has the appearance of lymphocyte infiltration within the thyroid tissue and the formation of lymphoid follicles/germinal centres within the thyroid
  - De Quervain's thyroiditis (granulomatous thyroiditis)
    - Has histologically granulomatous appearance due to macrophage infiltration
  - Riedel's thyroiditis (fibrosing thyroiditis)

        - Thyroid becomes hard to touch due to extensive fibrosis within the gland
- Multinodular goitre/toxic goitre
- Follicular adenoma and/or carcinoma
- Drug induced thyroid stimulation (amiodarone/thyroxine)
- TSH secreting tumour

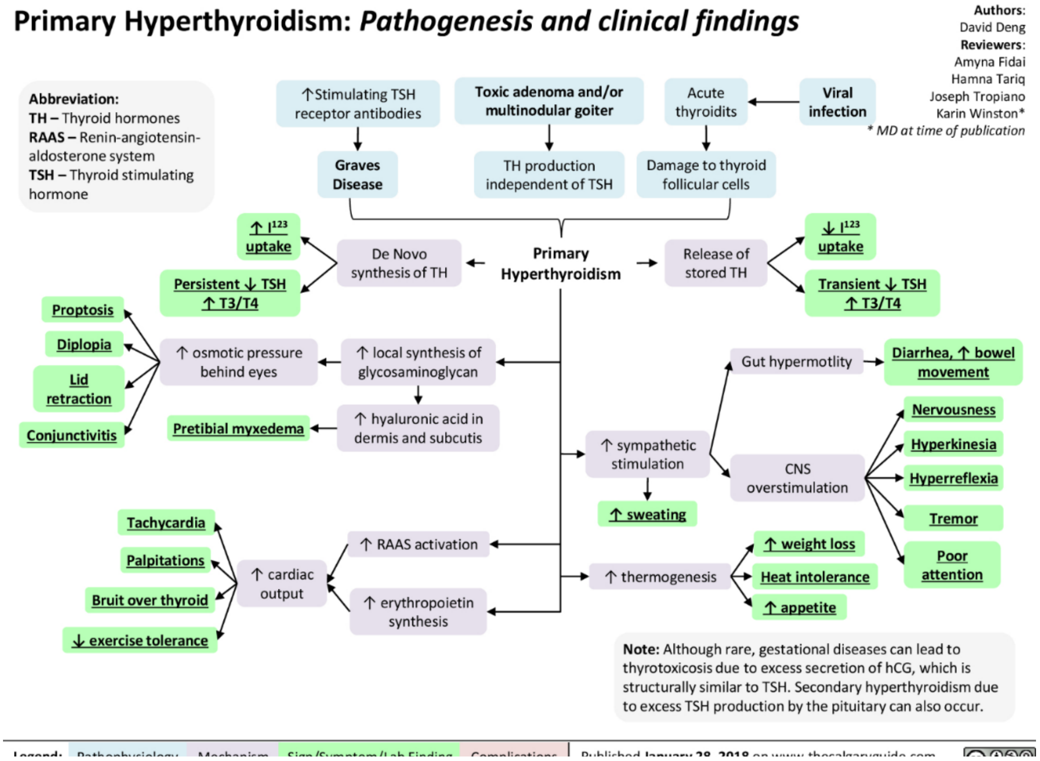
Thyroid function tests are used to investigate thyroid function:

- TSH is the most sensitive test for thyroid dysfunction
    - In hyperthyroidism, TSH will be reduced while thyroid hormone will be elevated
    - In hypothyroidism, TSH will be elevated while thyroid hormone will be reduced

Thyroid uptake scans can be used to assess thyroid functionalist.

- Radioactive technetium is used as it mimics iodine and is taken into the thyroid gland
- Overactive glands or nodules will glow a bright white, while darkness will be the major feature of underactive glands or nodules

Thyroid ultrasounds can be used as well and can be helpful in guiding FNA.



Primary Hyperthyroidism: *Pathogenesis and clinical findings*

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Abbreviation:
TH – Thyroid hormones
RAAS – Renin-angiotensin-aldosterone system
TSH – Thyroid stimulating hormone

↑Stimulating TSH receptor antibodies → **Graves Disease**

Toxic adenoma and/or multinodular goiter → TH production independent of TSH

Viral infection → Acute thyroidits → Damage to thyroid follicular cells

Primary Hyperthyroidism

De Novo synthesis of TH → **↑ I^{123} uptake**; **Persistent ↓ TSH ↑ T3/T4**

Release of stored TH → **↓ I^{123} uptake**; **Transient ↓ TSH ↑ T3/T4**

↑ local synthesis of glycosaminoglycan → ↑ osmotic pressure behind eyes → **Proptosis**, **Diplopia**, **Lid retraction**, **Conjunctivitis**

↑ local synthesis of glycosaminoglycan → ↑ hyaluronic acid in dermis and subcutis → **Pretibial myxedema**

↑ sympathetic stimulation → **↑ sweating**

↑ sympathetic stimulation → Gut hypermotlity → **Diarrhea, ↑ bowel movement**

↑ sympathetic stimulation → CNS overstimulation → **Nervousness**, **Hyperkinesia**, **Hyperreflexia**, **Tremor**, **Poor attention**

↑ thermogenesis → **↑ weight loss**, **Heat intolerance**, **↑ appetite**

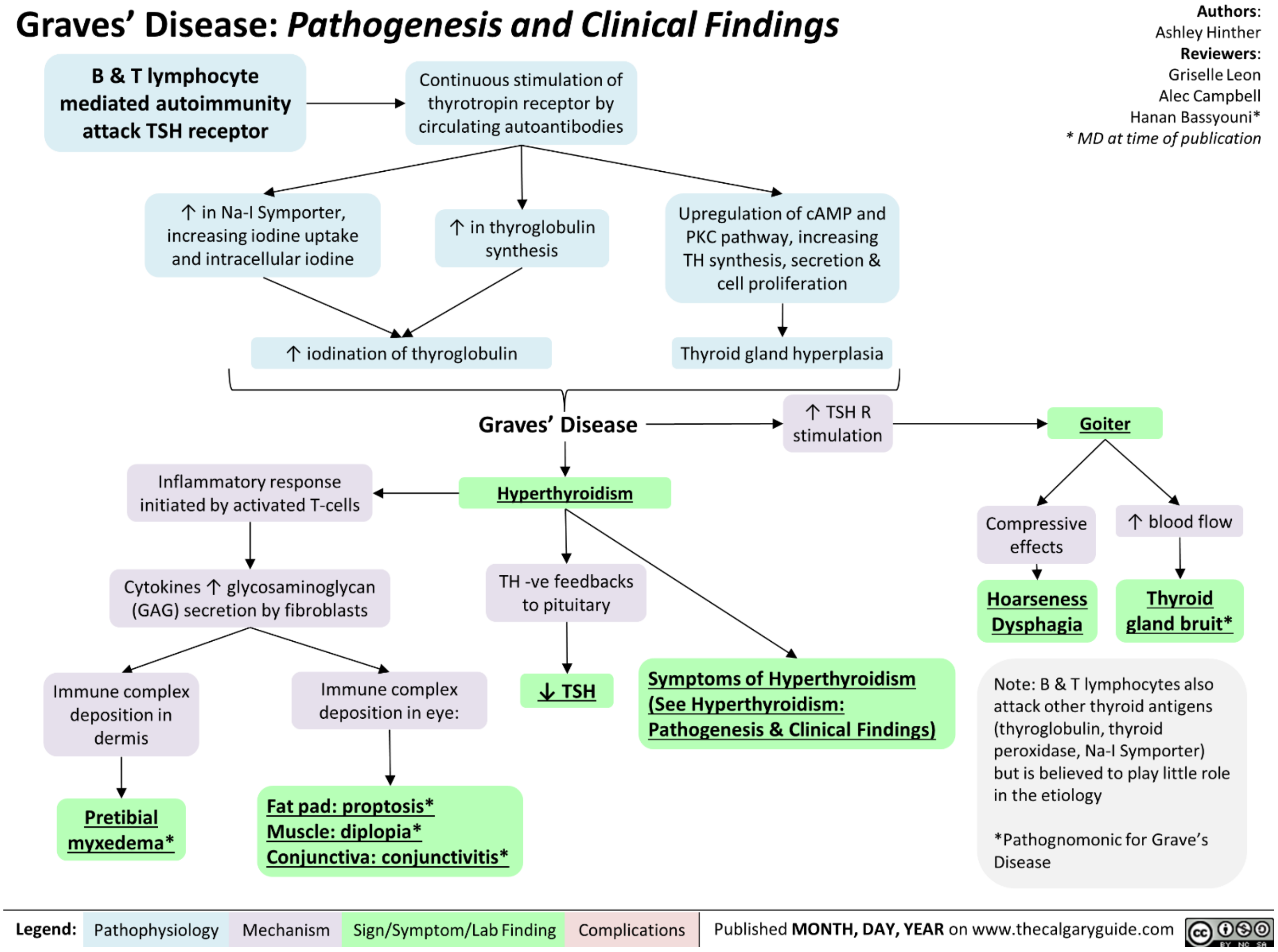
↑ RAAS activation → ↑ cardiac output

↑ erythropoietin synthesis → ↑ cardiac output

↑ cardiac output → **Tachycardia**, **Palpitations**, **Bruit over thyroid**, **↓ exercise tolerance**

Note: Although rare, gestational diseases can lead to thyrotoxicosis due to excess secretion of hCG, which is structurally similar to TSH. Secondary hyperthyroidism due to excess TSH production by the pituitary can also occur.

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications | Published **January 28, 2018** on www.thecalgaryguide.com



Graves' Disease: *Pathogenesis and Clinical Findings*

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** MD at time of publication*

B & T lymphocyte mediated autoimmunity attack TSH receptor → Continuous stimulation of thyrotropin receptor by circulating autoantibodies

Continuous stimulation of thyrotropin receptor by circulating autoantibodies → ↑ in Na-I Symporter, increasing iodine uptake and intracellular iodine; ↑ in thyroglobulin synthesis; Upregulation of cAMP and PKC pathway, increasing TH synthesis, secretion & cell proliferation

↑ in Na-I Symporter … and ↑ in thyroglobulin synthesis → ↑ iodination of thyroglobulin

Upregulation of cAMP and PKC pathway … → Thyroid gland hyperplasia

↑ iodination of thyroglobulin; Thyroid gland hyperplasia → **Graves' Disease**

Graves' Disease → ↑ TSH R stimulation → **Goiter**

Goiter → Compressive effects → **Hoarseness Dysphagia**

Goiter → ↑ blood flow → **Thyroid gland bruit***

Graves' Disease → **Hyperthyroidism**

Hyperthyroidism → TH -ve feedbacks to pituitary → **↓ TSH**

Hyperthyroidism → **Symptoms of Hyperthyroidism (See Hyperthyroidism: Pathogenesis & Clinical Findings)**

Hyperthyroidism → Inflammatory response initiated by activated T-cells → Cytokines ↑ glycosaminoglycan (GAG) secretion by fibroblasts

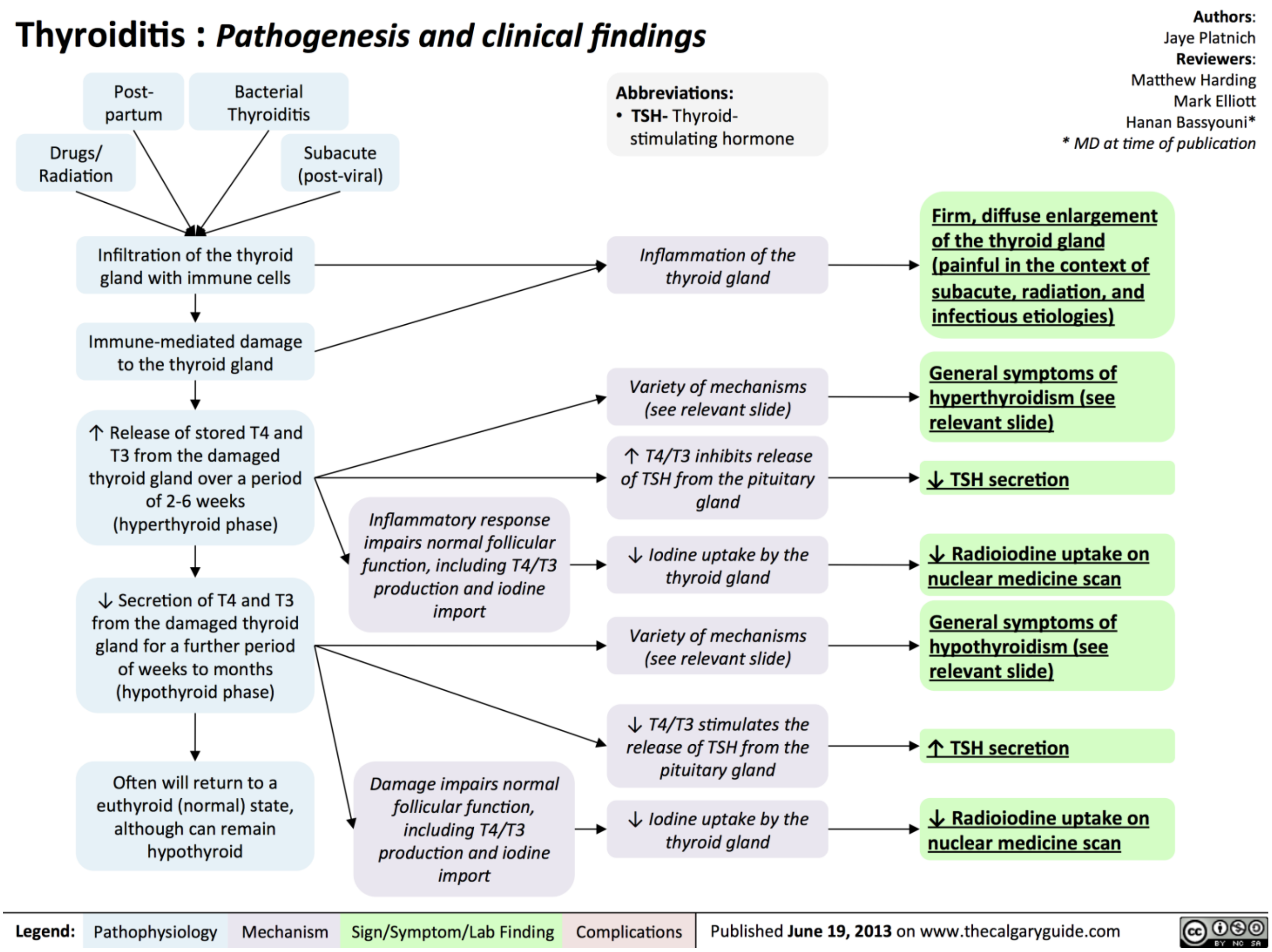
Cytokines ↑ glycosaminoglycan (GAG) secretion by fibroblasts → Immune complex deposition in dermis → **Pretibial myxedema***

Cytokines ↑ glycosaminoglycan (GAG) secretion by fibroblasts → Immune complex deposition in eye: → **Fat pad: proptosis*** **Muscle: diplopia*** **Conjunctiva: conjunctivitis***

Note: B & T lymphocytes also attack other thyroid antigens (thyroglobulin, thyroid peroxidase, Na-I Symporter) but is believed to play little role in the etiology

*Pathognomonic for Grave's Disease

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications | Published **MONTH, DAY, YEAR** on www.thecalgaryguide.com



Thyroiditis : ***Pathogenesis and clinical findings***

Authors:
Jaye Platnich
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Abbreviations:
- **TSH-** Thyroid-stimulating hormone

Post-partum
Bacterial Thyroiditis
Drugs/ Radiation
Subacute (post-viral)

Infiltration of the thyroid gland with immune cells → *Inflammation of the thyroid gland* → **Firm, diffuse enlargement of the thyroid gland (painful in the context of subacute, radiation, and infectious etiologies)**

Immune-mediated damage to the thyroid gland → *Inflammation of the thyroid gland*

↑ Release of stored T4 and T3 from the damaged thyroid gland over a period of 2-6 weeks (hyperthyroid phase)
→ *Variety of mechanisms (see relevant slide)* → **General symptoms of hyperthyroidism (see relevant slide)**
→ *↑ T4/T3 inhibits release of TSH from the pituitary gland* → **↓ TSH secretion**
→ *Inflammatory response impairs normal follicular function, including T4/T3 production and iodine import* → *↓ Iodine uptake by the thyroid gland* → **↓ Radioiodine uptake on nuclear medicine scan**

↓ Secretion of T4 and T3 from the damaged thyroid gland for a further period of weeks to months (hypothyroid phase)
→ *Variety of mechanisms (see relevant slide)* → **General symptoms of hypothyroidism (see relevant slide)**
→ *↓ T4/T3 stimulates the release of TSH from the pituitary gland* → **↑ TSH secretion**
→ *Damage impairs normal follicular function, including T4/T3 production and iodine import* → *↓ Iodine uptake by the thyroid gland* → **↓ Radioiodine uptake on nuclear medicine scan**

Often will return to a euthyroid (normal) state, although can remain hypothyroid

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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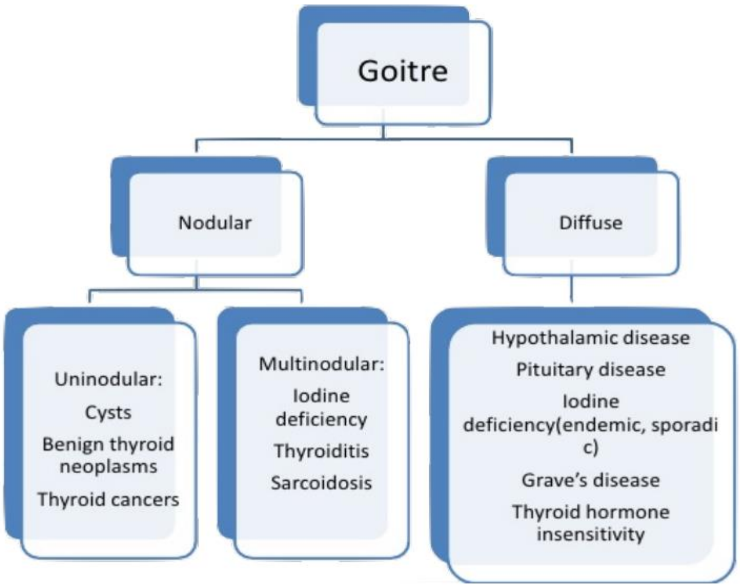
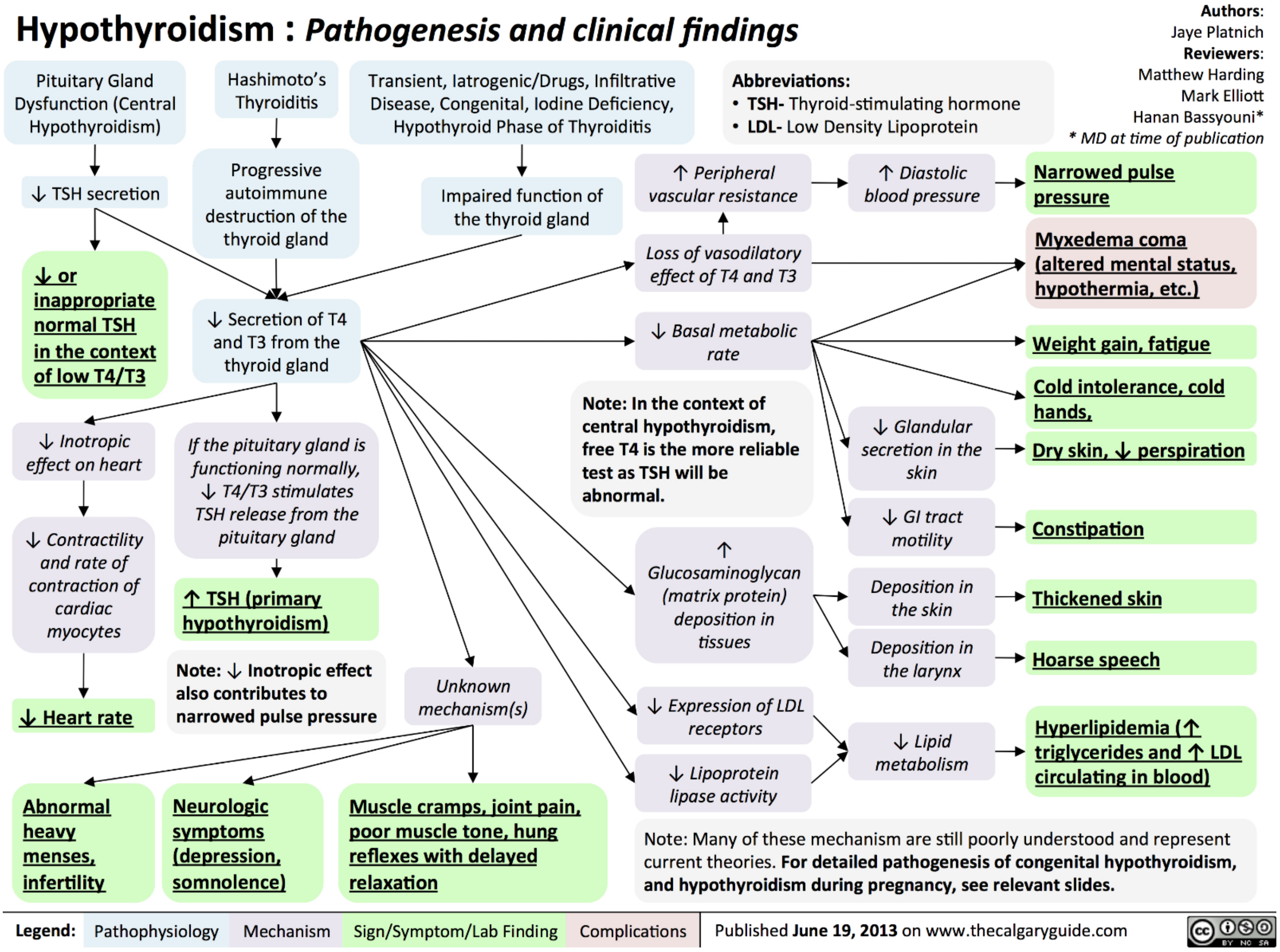
Thyroid disease treatment involves management of the thyroid imbalance.

- Hyperthyroidism can be treated with anti-thyroid drugs
    - These usually work by inhibiting thyroperoxidase to prevent the oxidation of iodide within the thyroid, preventing the production of thyroglobulin
    - Methimazole is a key anti-thyroid drug
        - This is a teratogen and is contraindicated in pregnancy
- Hyperthyroid symptoms are often also treated with beta blockers (particularly propranolol)
- Hyperthyroidism can also be treated with a thyroidectomy (particularly in malignancies or in cases of airway/oesophagus occlusion) or with radioactive iodine
- Hypothyroidism is treated with exogenous thyroxine
    - Some patients will opt for removal in hyperthyroidism and are then treated with thyroxine





Hypothyroidism : *Pathogenesis and clinical findings*

Authors:
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Reviewers:
Matthew Harding
Mark Elliott
Hanan Bassyouni*
** MD at time of publication*

Abbreviations:
- **TSH-** Thyroid-stimulating hormone
- **LDL-** Low Density Lipoprotein

Pituitary Gland Dysfunction (Central Hypothyroidism)

↓ TSH secretion

↓ or inappropriate normal TSH in the context of low T4/T3

Hashimoto's Thyroiditis

Progressive autoimmune destruction of the thyroid gland

Transient, Iatrogenic/Drugs, Infiltrative Disease, Congenital, Iodine Deficiency, Hypothyroid Phase of Thyroiditis

Impaired function of the thyroid gland

↓ Secretion of T4 and T3 from the thyroid gland

↓ Inotropic effect on heart

↓ Contractility and rate of contraction of cardiac myocytes

↓ Heart rate

If the pituitary gland is functioning normally, ↓ T4/T3 stimulates TSH release from the pituitary gland

↑ TSH (primary hypothyroidism)

Note: ↓ Inotropic effect also contributes to narrowed pulse pressure

Unknown mechanism(s)

Abnormal heavy menses, infertility

Neurologic symptoms (depression, somnolence)

Muscle cramps, joint pain, poor muscle tone, hung reflexes with delayed relaxation

↑ Peripheral vascular resistance

↑ Diastolic blood pressure

Narrowed pulse pressure

Loss of vasodilatory effect of T4 and T3

Myxedema coma (altered mental status, hypothermia, etc.)

↓ Basal metabolic rate

Weight gain, fatigue

Cold intolerance, cold hands,

Note: In the context of central hypothyroidism, free T4 is the more reliable test as TSH will be abnormal.

↓ Glandular secretion in the skin

Dry skin, ↓ perspiration

↓ GI tract motility

Constipation

↑ Glucosaminoglycan (matrix protein) deposition in tissues

Deposition in the skin

Thickened skin

Deposition in the larynx

Hoarse speech

↓ Expression of LDL receptors

↓ Lipoprotein lipase activity

↓ Lipid metabolism

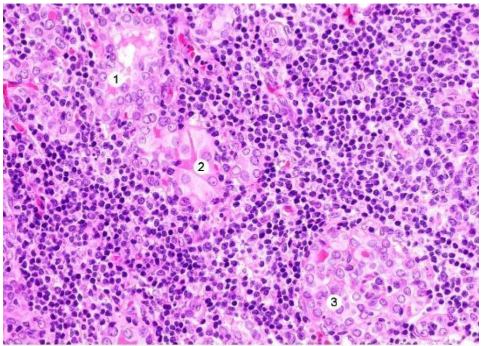
Hyperlipidemia (↑ triglycerides and ↑ LDL circulating in blood)

Note: Many of these mechanism are still poorly understood and represent current theories. **For detailed pathogenesis of congenital hypothyroidism, and hypothyroidism during pregnancy, see relevant slides.**

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

Published **June 19, 2013** on www.thecalgaryguide.com

Hypothyroidism occurs when there is a decrease in thyroid hormone production. This has a number of characteristic signs and symptoms which include:



Hashimoto's thyroiditis, evolution of squamous metaplasia: (1) colloid-containing follicle, (2) cell enlargement, prominent eosinophilia, (3) crowding, loss of colloid and follicular space, distinct cell borders (H&E, ×40)

- Fatigue and low energy
- Unexplained weight gain
- Malar flush
- Depression
- Intellectual impairment (particularly memory loss)
- Bradycardia
- Intolerance to cold
- Puffy face (due to myxoedema)
- Dry skin
- Hair loss
- Myxoedema
    - This occurs due to subcutaneous hyaluronic acid deposits
    - This is different to pretibial myxoedema which occurs only in Grave's Disease
- Goitre
- Hypothyroid myopathy
    - This occurs due to increased serum potassium levels
- Hyponatremia

There are a number of causes of hypothyroidism. These include:

- Primary hyperthyroidism (issues affecting the thyroid gland directly)
    - Iodine deficiency
        - Occurs most commonly in iodine deplete countries
    - Destruction of the thyroid gland
    - Hashimoto's thyroiditis
        - This is most common cause of hypothyroidism in iodine replete countries
        - Gland destruction occurs due to autoimmune reactions resulting in an initial release of thyroid hormone that can sometimes cause initial hyperthyroid symptoms due to the release of thyroid hormone from damaged follicles
            - After gland destruction occurs hypothyroidism results and the thyroid loses its follicular appearance.
    - Genetic, drug induced etc. impaired thyroid hormone synthesis
        - Iatrogenic hypothyroidism is largely caused by thyroidectomy for hyperthyroid conditions
            - This is because hypothyroidism is easier to treat than hyperthyroidism

        - Maternal hypothyroidism
        - Wolf-Chaikoff effect: excess iodine in the diet causes inhibition of MIT and DIT synthesis resulting in goitre and hypothyroidism (rare)
- Secondary hyperthyroidism
    - Pituitary disorder resulting in decreased TSH secretion
        - This can include a non-functional adenoma as well as a functional adenoma of a different cell type that compresses the thyroid and impacts function of thyrotrophs
    - Infection
    - Pituitary destruction or injury
    - Genetic conditions
- Tertiary hypothyroidism
    - Hypothalamic disorder resulting in decreased thyroid releasing hormone production

Treatment of hypothyroidism is almost always administration of exogenous T4.

- T4 is used because the administration of T3 causes an increased likelihood of entering into hyperthyroid states and because the body can easily convert it into T3 as required

CONGENITAL THYROID DISORDERS

The development of the thyroid gland begins early in foetal life. The path of development results in a number of characteristic congenital issues. These include:

- Ectopic thyroid: the thyroid gland descent fails, and the gland grows (and functions normally) in an abnormal place along the path of descent
    - Lingual thyroid is an ectopic thyroid condition that occurs when the thyroid gland grows at the base of the tongue (can obstruct air and food and becomes an issue)
- Thyroglossal cyst: the thyroglossal duct (along the path of development) fails to close fully and can fill with fluid at a later point in life, resulting in a cyst.
- Thyroid agenesis
- Congenital hypothyroidism: occurs when the infant is unable to produce thyroid gland due to a thyroid defect or enzyme defect (usually due to defective TPO) or because of an iodine deficiency.
    - Congenital abnormalities leading to hypothyroidism can result in cretinism if not treated; they can be easily treated with thyroxine at birth
- Cretinism: severely stunted mental and physical development due to maternal hypothyroidism or neonatal hypothyroidism. This was once a common condition worldwide but now is only seen in iodine deplete countries due to supplementation of foods in the developed world.
    - Cretinism in the developed world is very treatable; neonates are tested for hypothyroidism at birth via heel prick and can be administered exogenous T4
    - This results in an almost total recovery

THYROID TUMOURS

Thyroid tumours can be both benign or malignant and functional or non-functional. Nodular goitres or solitary nodules are usually assessed via fine needle aspiration and the requirement for removal is assessed based on the results. A low cellularity and high level of colloid is normal, which decreased colloid and extra cellularity is suspicious. Other features include dysplastic cells and the grooved nuclei of papillary carcinoma. Nodules are more likely to be malignant when they are hard and focal, non-functional or present with associated lymphadenopathy. The most common presentation of thyroid tumours is a relatively small, painless nodule.

Risk factors for thyroid malignancy include:

- Exposure to ionising radiation
- Familial history of endocrine tumours
- MEN2 syndrome

Tumours are less likely to be malignancy if:

- The goitre is diffuse
- The nodule is 'hot' or functioning
    - Nodules can be assessed using a thyroid uptake can which assess the functionality of cellular areas. Areas of high functionality are considered 'hot' and functionality is usually not preserved in malignancy.
- The nodule is tender

Types of thyroid tumours include:

- Benign neoplasia/follicular adenoma
    - Well-formed nodule without fibrous capsule
    - Histologically appears microfollicular with evident retained architecture
    - No dysplastic signs
    - It can often be difficult to distinguish between adenoma or carcinoma via FNA because of the key differences being seen in the fibrous capsule of the tumour
        - For this reason, most small nodules suspected to be adenomas are initially observed for a period of time before surgical removal being indicated
- Papillary carcinoma (accounts for 80% of malignancies)
    - Can be solitary or multiple nodules
    - May present with fibrosis and/or calcification (known as psammoma bodies)
    - Have a papillary growth pattern to follicles (when still present)
        - This refers to a finger-like growth pattern
    - Histological appearance of follicular cells includes grooved nuclei and vacuolated appearance
        - The vacuolated nuclei are often described as orphan Annie eye nuclei
    - A key risk factor for this cancer is previous radiation exposure (i.e. very common in survivors of Hiroshima and Chernobyl)
    - This malignancy can be diagnosed on FNA and has a good prognosis
    - Treatment usually involves administration of radioactive iodine and/or surgery
- Follicular carcinoma
    - Have a fibrous tumour capsule surrounding the growth through which it often invades

    - Have a relatively retained architecture but with little follicles
    - Degree of capsular and vascular invasion determines malignancy in most cases due to similarity to follicular adenoma
- Medullary carcinoma
    - This cancer is derived from the C cells of the thyroid interstitium
    - Abnormally shaped cells arranged in nests with no follicular architecture present
    - Deposition of amyloid in the stoma will be present
        - The amyloid is a result of calcitonin production (a protein substance)
    - Patients often experience hypocalcaemia due to the excess production of calcitonin

PARATHYROID PATHOLOGY

Parathyroid glands are most usually overactive, causing hyperparathyroidism. Hypoparathyroidism is uncommon and usually due to iatrogenic causes such as thyroidectomy but can also be autoimmune. Hyperparathyroidism is usually divided into primary and secondary causes:

- Primary:
    - Parathyroid adenoma, hyperplasia or carcinoma
        - Histologically this usually appears as a hypercellular parathyroid gland with decreased fat content. Usually the cellular content will be centred in one location of the gland.
    - MEN1 or MEN2 syndrome
- Secondary
    - Renal failure
        - Results in reduced vitamin D activation, lower calcium and increased PTH
    - PTH secreting tumour
    - Hyperphosphatemia
    - Decreased calcium intake due to low oral intake, vitamin D deficiency etc.
    - Inhibition of bone resorption due to bisphosphates etc.

PTH	Serum calcium	Likely type
high	high	primary hyperparathyroidism
high	low or normal	secondary hyperparathyroidism

Primary hyperparathyroidism causes elevated calcium levels and is usually defined by;

- Bones: bone pain and fractures due to osteoporosis
- Moans: fatigue and confusion
- Abdominal groans: renal stones and constipation
    - Pain occurs due to excess PTH causing ileus

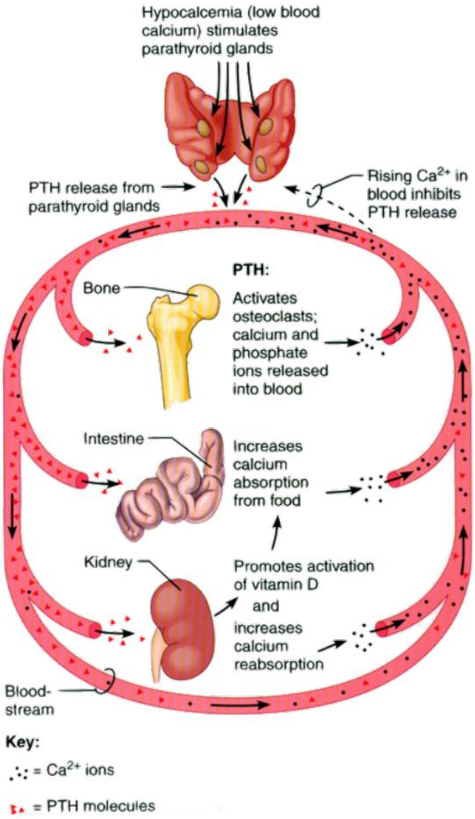
Hypoparathyroidism is defined by:

- Neuromuscular excitability
    - Cvoeste's sign: tapping near the ear resulting in facial twitching
    - Trousseau's sign: maintaining BP cuff inflation causes spasm of the hand
- Seizures
- Cramping or tetany
- Anxiety
- Paraesthesia

Investigations into parathyroid abnormalities involve:

- PTH levels and calcium levels
    - High in hyperparathyroidism and low in hypoparathyroidism
- 24-hour urinary excretion of calcium
- Localised imaging (ultrasound or parathyroid uptake scan)
- DEXA scan to investigate for osteoporosis

Treatment of hyperparathyroidism usually involves surgical excision of the affect gland(s) but if surgery is not appropriate bisphosphates can be used to prevent bone resorption. Treatment of hypoparathyroidism involves oral calcitriol (activated Vit D) and causes some calcium absorption from the kidney and gut. This is usually combined with oral calcium supplementation.


Hypocalcemia (low blood calcium) stimulates parathyroid glands
PTH release from parathyroid glands
Rising Ca²⁺ in blood inhibits PTH release
PTH:
Bone
Activates osteoclasts; calcium and phosphate ions released into blood
Intestine
Increases calcium absorption from food
Kidney
Promotes activation of vitamin D
and
increases calcium reabsorption
Blood-stream
Key:
= Ca²⁺ ions
= PTH molecules

MEN SYNDROMES

MEN is an abbreviation for multiple endocrine neoplasia and is a group of three autosomal dominant syndromes associated with specific types of neoplasia.

- MEN1 is caused by altered men expression
    - Causes primary hyperparathyroidism, pancreatic tumours, pituitary adenomas
    - I.e. Three P's – parathyroid, pancreas, pituitary
- MEN2 is caused by altered expression of RET proto-oncogene causing elevated tyrosine kinase activity
    - Causes medullary thyroid carcinoma, pheochromocytoma and primary hyperparathyroidism.
    - I.e. One M and 2 Ps – medullary, parathyroid and pheochromocytoma.

These run in families and should be investigated when a patient presents with multiple endocrine tumours. The tumours can be both benign and malignant.

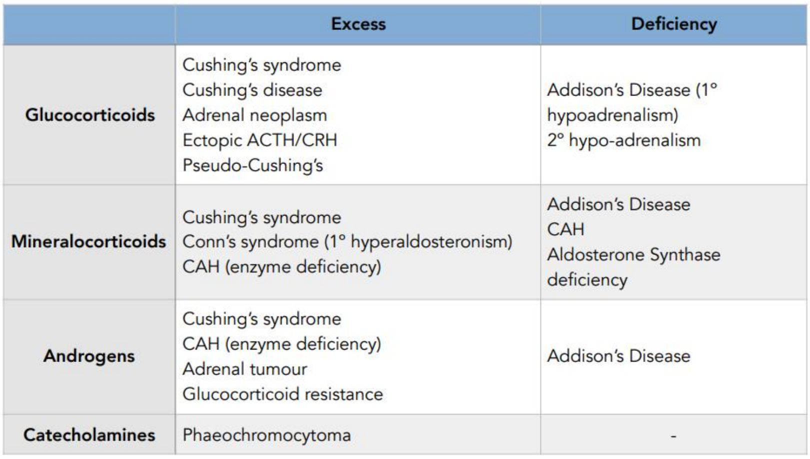
ADRENAL PATHOLOGY

Impairment of the adrenal medulla is extremely rare, Deficiency can be caused by a congenital absence of the medulla (i.e. failure to develop) or a hereditary deficiency of enzymes involved in catecholamine synthesis. Excess is usually caused by neoplasms. Excess is more common than deficiency.

PHEOCHROMOCYTOMA

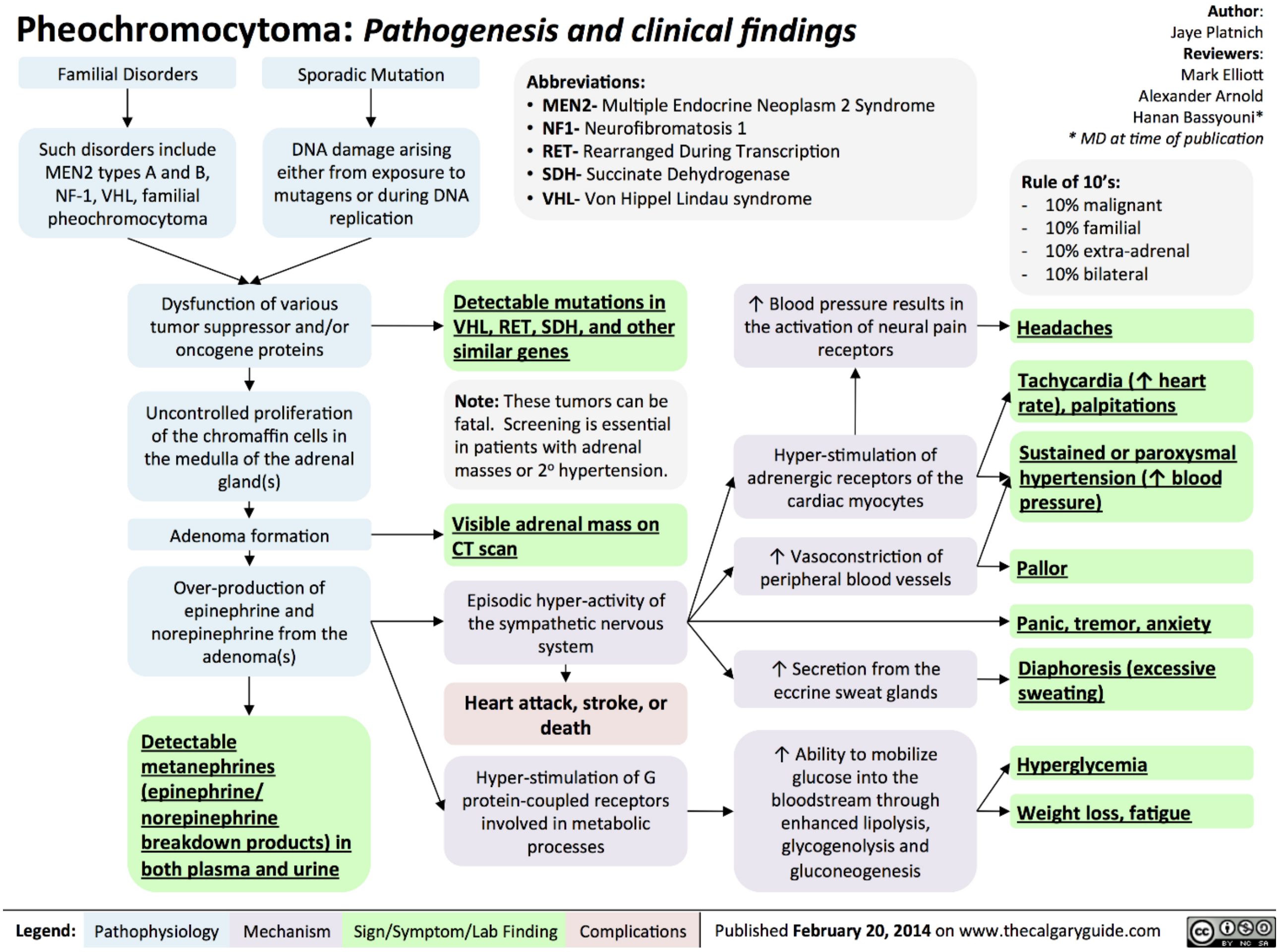
Pheochromocytoma is the name given to a neoplasm of the adrenal medulla. It causes a loss of the coordinated control of catecholamine synthesis.

- This is a functional neoplasm, thus produces high levels of catecholamines



	Excess	Deficiency
Glucocorticoids	Cushing's syndrome Cushing's disease Adrenal neoplasm Ectopic ACTH/CRH Pseudo-Cushing's	Addison's Disease (1° hypoadrenalism) 2° hypo-adrenalism
Mineralocorticoids	Cushing's syndrome Conn's syndrome (1° hyperaldosteronism) CAH (enzyme deficiency)	Addison's Disease CAH Aldosterone Synthase deficiency
Androgens	Cushing's syndrome CAH (enzyme deficiency) Adrenal tumour Glucocorticoid resistance	Addison's Disease
Catecholamines	Phaeochromocytoma	-

- Clinical features of pheochromocytoma include:
    - Paroxysmal hypertension that is difficult to control
    - Headaches
    - Sweating
    - Tachycardia
    - Anxiety and nervousness
    - Palpitations
- The clinical triad most commonly seen includes headaches, sweating and tachycardia.
- A pheochromocytoma can also develop in extra-adrenal areas, such as the sympathetic chain ganglion. These are known as paragangliomas but have the same symptoms and treatment as a standard medullary neoplasm.
- Diagnosis is based on excess catecholamine secretion followed by imaging
    - This can be achieved using 24-hour urine catecholamines as well as free plasma metanepherines
        - Metanepherines are the metabolites of catecholamines that have a longer half life and are thus easier to measure
    - Imaging usually involves CT/MRI/PET scan
    - Genetic testing for MEN syndromes is indicated in some patients
- Treatment involves pharmacological inhibition of catecholamines to prevent surges (i.e. alpha and beta blockers) followed by surgical excision of the tumour



Pheochromocytoma: ***Pathogenesis and clinical findings***

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Abbreviations:
- **MEN2-** Multiple Endocrine Neoplasm 2 Syndrome
- **NF1-** Neurofibromatosis 1
- **RET-** Rearranged During Transcription
- **SDH-** Succinate Dehydrogenase
- **VHL-** Von Hippel Lindau syndrome

Rule of 10's:
- 10% malignant
- 10% familial
- 10% extra-adrenal
- 10% bilateral

Familial Disorders → Such disorders include MEN2 types A and B, NF-1, VHL, familial pheochromocytoma

Sporadic Mutation → DNA damage arising either from exposure to mutagens or during DNA replication

Dysfunction of various tumor suppressor and/or oncogene proteins → **Detectable mutations in VHL, RET, SDH, and other similar genes**

Uncontrolled proliferation of the chromaffin cells in the medulla of the adrenal gland(s)

Adenoma formation → **Visible adrenal mass on CT scan**

Note: These tumors can be fatal. Screening is essential in patients with adrenal masses or 2° hypertension.

Over-production of epinephrine and norepinephrine from the adenoma(s) → **Detectable metanephrines (epinephrine/ norepinephrine breakdown products) in both plasma and urine**

Episodic hyper-activity of the sympathetic nervous system → **Heart attack, stroke, or death**

Hyper-stimulation of adrenergic receptors of the cardiac myocytes → ↑ Blood pressure results in the activation of neural pain receptors → **Headaches**

Tachycardia (↑ heart rate), palpitations

Sustained or paroxysmal hypertension (↑ blood pressure)

↑ Vasoconstriction of peripheral blood vessels → **Pallor**

Panic, tremor, anxiety

↑ Secretion from the eccrine sweat glands → **Diaphoresis (excessive sweating)**

Hyper-stimulation of G protein-coupled receptors involved in metabolic processes → ↑ Ability to mobilize glucose into the bloodstream through enhanced lipolysis, glycogenolysis and gluconeogenesis → **Hyperglycemia**, **Weight loss, fatigue**

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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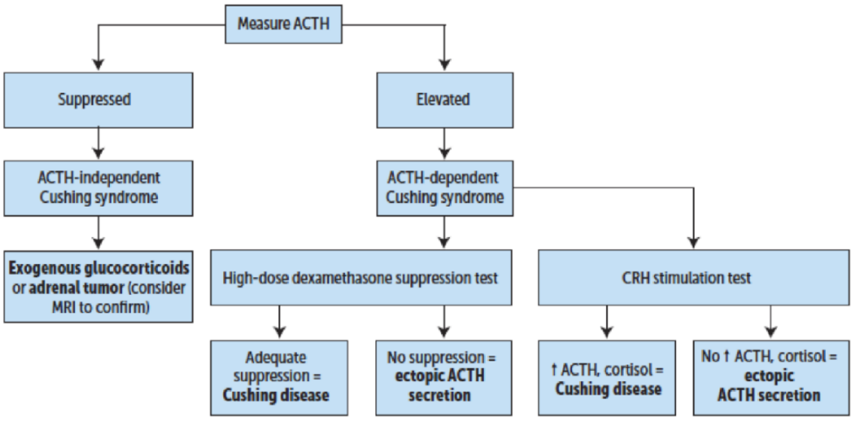
cc BY NC SA

HYPERALDOSTERONISM

This condition can be both primary (caused by an issue in the adrenal cortex itself) or secondary (usually due to the activation of the RAAS system, such as during decreased renal perfusion, hypovolemia or pregnancy). Primary causes include:

- Adrenocortical neoplasm
    - Usually causes Conn syndrome

- Bilateral idiopathic hyperaldosteronism
- Familial hyperaldosteronism


Measure ACTH
Suppressed
Elevated
ACTH-independent Cushing syndrome
ACTH-dependent Cushing syndrome
Exogenous glucocorticoids or adrenal tumor (consider MRI to confirm)
High-dose dexamethasone suppression test
CRH stimulation test
Adequate suppression = Cushing disease
No suppression = ectopic ACTH secretion
↑ ACTH, cortisol = Cushing disease
No ↑ ACTH, cortisol = ectopic ACTH secretion

Primary hyperaldosteronism causes:
- High aldosterone
- Low renin

Secondary hyperaldosteronism causes:
- High aldosterone
- High renin

Conn's syndrome (accounts for 90% of hyperaldosteronism) is usually caused by a solitary aldosterone-producing adenoma. It can also be caused by bilateral or unilateral hyperplasia or ectopic aldosterone-producing cancers. This is a condition defined by high levels of circulating aldosterone in the absence of a physiological reason for it. Symptoms include:
- Increased sodium retention and potassium excretion (hypernatremia)
    - This causes volume expansion and can lead to hypertension and oedema
- Hypokalaemia can lead to many symptoms such as headaches, muscle weakness, constipation
- Excessive thirst
- Metabolic alkalosis
    - This occurs because aldosterone upregulates excretion of H+

The classic triad of symptoms includes headaches, flushing and hypertension.

Investigations includes:
- Elevated serum sodium and low potassium
- Elevated aldosterone and suppressed renin
    - The aldosterone:renin ratio is also sometimes investigated

Treatment involves:
- Surgery if appropriate
    - Usually if tumour is unilateral
- Aldosterone receptor antagonists (spironolactone)

HYPERCORTISOLISM:

Excess cortisol levels are usually referred to as Cushing's syndrome. Cushing's syndrome can be both ACTH independent or dependant, depending on the levels of response to ACTH in the body. Cushing's syndrome is different to Cushing's disease – the disease refers specifically to the ACTH producing pituitary adenoma.

ACTH independent causes include:
- Adrenal neoplasm
- Aberrant receptor expression
- Iatrogenic
    - Exogenous administration of glucocorticoids is the most common cause of Cushing's syndrome

ACTH dependant causes include:
- Pituitary adenoma
- Ectopic ACTH secretion (usually due to paraneoplastic syndrome, usually as a result of lung cancer)
- Ectopic CRH secretion

Symptoms of Cushing's syndrome include:
- Unexplained weight gain
- Central obesity with thin arms and legs
- Hypertension
- Facial plethora (redness and puffiness)
- Proximal muscle weakness
- Glucose intolerance (may have diabetes mellitus)
- Decreased libido
- Depression
- Osteoporosis
- Easy bruising due to thinning of the skin
- Menstrual disorders
    - This occurs because increased ACTH can have a downregulatory effect on the release of FSH and LH
- Hypercholesterolemia
- Striae
- Acne and/or hirsutism

Investigations in Cushing's disease must be aware of the diurnal rhythm of cortisol production and of the fact that 95% of circulating cortisol is bound to CBG. For this reason, investigations are usually completed at a standard time (i.e. 11pm, 8am). 24-hour urine free cortisol can also be used but is often more difficult for the patient.

To investigate the cause of hypercortisolism, a dexamethasone suppression test is used. This is an exogenous glucocorticoid which should suppress ACTH production when administered, resulting in lowered cortisol if the HPA axis is functional.
- Correct suppression can be used to exclude Cushing's syndrome

- Incorrect suppression indicates Cushing's syndrome and a high-dose dexamethasone test is repeated, along with ACTH levels.
    - Low ACTH with no suppression of cortisol indicates a primary cause of Cushing's
    - Normal or high ACTH with no suppression indicates ectopic ACTH secretion
    - Normal or high ACTH with suppression indicates Cushing's disease (pituitary adenoma)
        - This occurs because pituitary adenomas respond only to high levels of dexamethasone but not to low levels
- Investigations also involve demonstrating elevated serum sodium and low potassium
- Confirmatory testing involves imagine

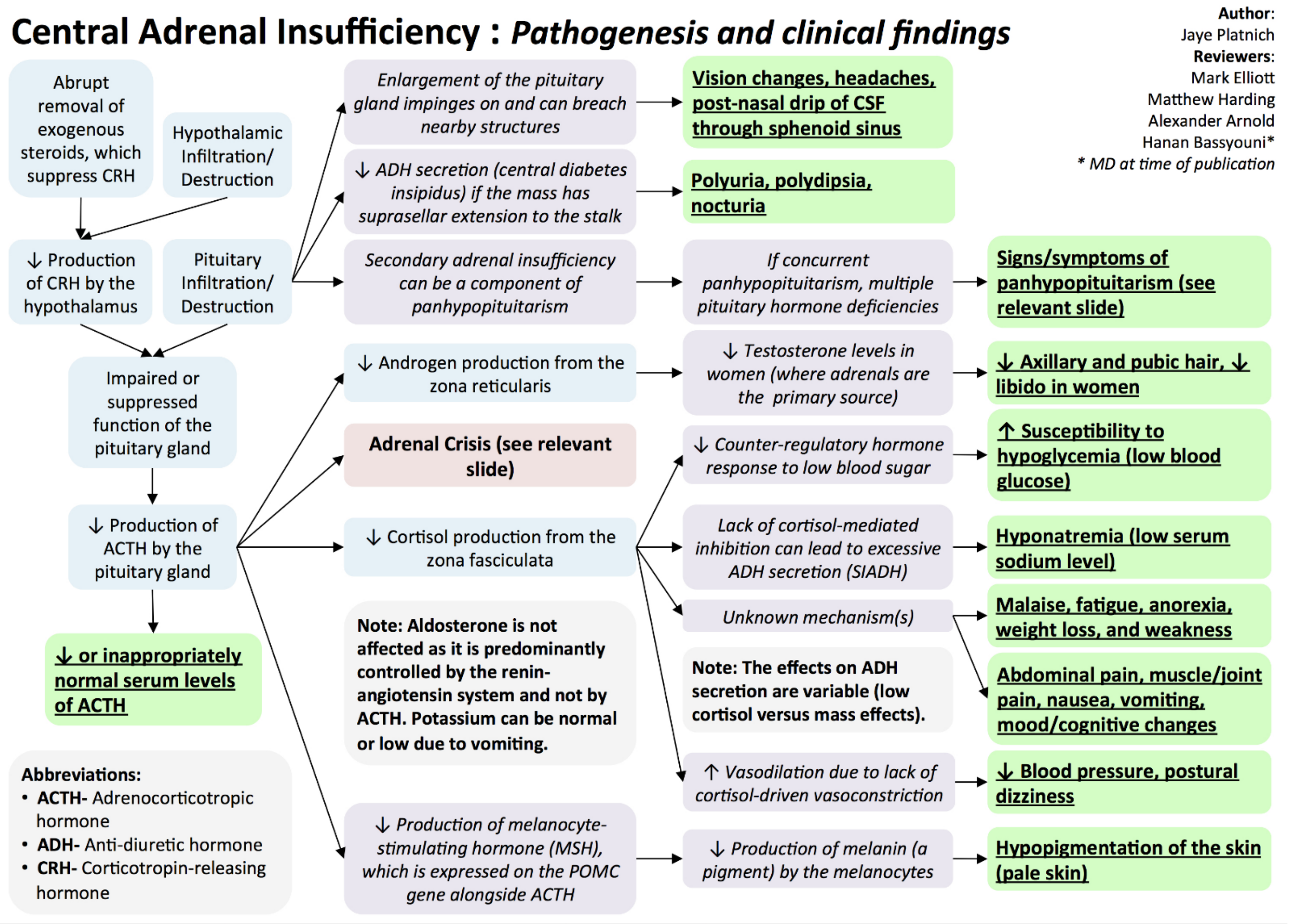
Treatment involves removal of the tumour when possible.

HYPOADRENALISM

This is also known as adrenal insufficiency. It can be both primary and secondary.

- Primary adrenal insufficiency is known as Addison's disease and will show:
    - Low cortisol
    - Low aldosterone
    - High ACTH
- Secondary adrenal insufficiency occurs because of pituitary ACTH failure and will show:
    - Low cortisol
    - Aldosterone levels normal
        - This occurs because the zona glomerulosa cells are intact and can respond to RAAS system activation
    - Low ACTH

Hypoadrenalism can be both chronic and acute and usually affects all three layers of the adrenal cortex.



Central Adrenal Insufficiency : *Pathogenesis and clinical findings*

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Abrupt removal of exogenous steroids, which suppress CRH

Hypothalamic Infiltration/ Destruction

↓ Production of CRH by the hypothalamus

Pituitary Infiltration/ Destruction

Impaired or suppressed function of the pituitary gland

↓ Production of ACTH by the pituitary gland

↓ or inappropriately normal serum levels of ACTH

Abbreviations:
- **ACTH-** Adrenocorticotropic hormone
- **ADH-** Anti-diuretic hormone
- **CRH-** Corticotropin-releasing hormone

Enlargement of the pituitary gland impinges on and can breach nearby structures

Vision changes, headaches, post-nasal drip of CSF through sphenoid sinus

↓ ADH secretion (central diabetes insipidus) if the mass has suprasellar extension to the stalk

Polyuria, polydipsia, nocturia

Secondary adrenal insufficiency can be a component of panhypopituitarism

If concurrent panhypopituitarism, multiple pituitary hormone deficiencies

Signs/symptoms of panhypopituitarism (see relevant slide)

↓ Androgen production from the zona reticularis

↓ Testosterone levels in women (where adrenals are the primary source)

↓ Axillary and pubic hair, ↓ libido in women

Adrenal Crisis (see relevant slide)

↓ Counter-regulatory hormone response to low blood sugar

↑ Susceptibility to hypoglycemia (low blood glucose)

↓ Cortisol production from the zona fasciculata

Lack of cortisol-mediated inhibition can lead to excessive ADH secretion (SIADH)

Hyponatremia (low serum sodium level)

Unknown mechanism(s)

Malaise, fatigue, anorexia, weight loss, and weakness

Abdominal pain, muscle/joint pain, nausea, vomiting, mood/cognitive changes

Note: Aldosterone is not affected as it is predominantly controlled by the renin-angiotensin system and not by ACTH. Potassium can be normal or low due to vomiting.

Note: The effects on ADH secretion are variable (low cortisol versus mass effects).

↑ Vasodilation due to lack of cortisol-driven vasoconstriction

↓ Blood pressure, postural dizziness

↓ Production of melanocyte-stimulating hormone (MSH), which is expressed on the POMC gene alongside ACTH

↓ Production of melanin (a pigment) by the melanocytes

Hypopigmentation of the skin (pale skin)

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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BY NC SA

- Acute hypoadrenalism (i.e. adrenal crisis) can occur when there is a sudden withdrawal of corticosteroid therapy. This is also known as a tertiary adrenal insufficiency because its cause is an iatrogenic suppression of the HPA axis resulting in impairment.
- Secondary hypoadrenalism can be caused by pituitary or hypothalamic abnormalities as well as glucocorticoid withdrawal

Addison's Disease is the name given to chronic adrenal insufficiency. It can be caused by:

- Autoimmune adrenalitis
    - Usually occurs because of antibodies directed at the 17a-hydroxylase enzyme or 21-b hydroxylase enzyme
- Infectious adrenalitis: usually caused by TB infiltration or meningitis
- Adrenal haemorrhage
- Adrenal tumour
- Adrenalectomy

Symptoms of Addison's disease include:

- Cortisol deficiency: fatigue, abdominal pain, nausea, vomiting

- Aldosterone deficiency: postural hypotension and dehydration
- Elevated ACTH: skin pigmentation particularly around mucosa and skin creases
    - This occurs because ACTH causes increased release of MSH

Primary Adrenal Insufficiency : *Clinical findings*

Abbreviations:
- **ACTH -** Adrenocorticotropic hormone
- **MSH -** Melanocyte-stimulating hormone
- **RTA -** Renal tubular acidosis

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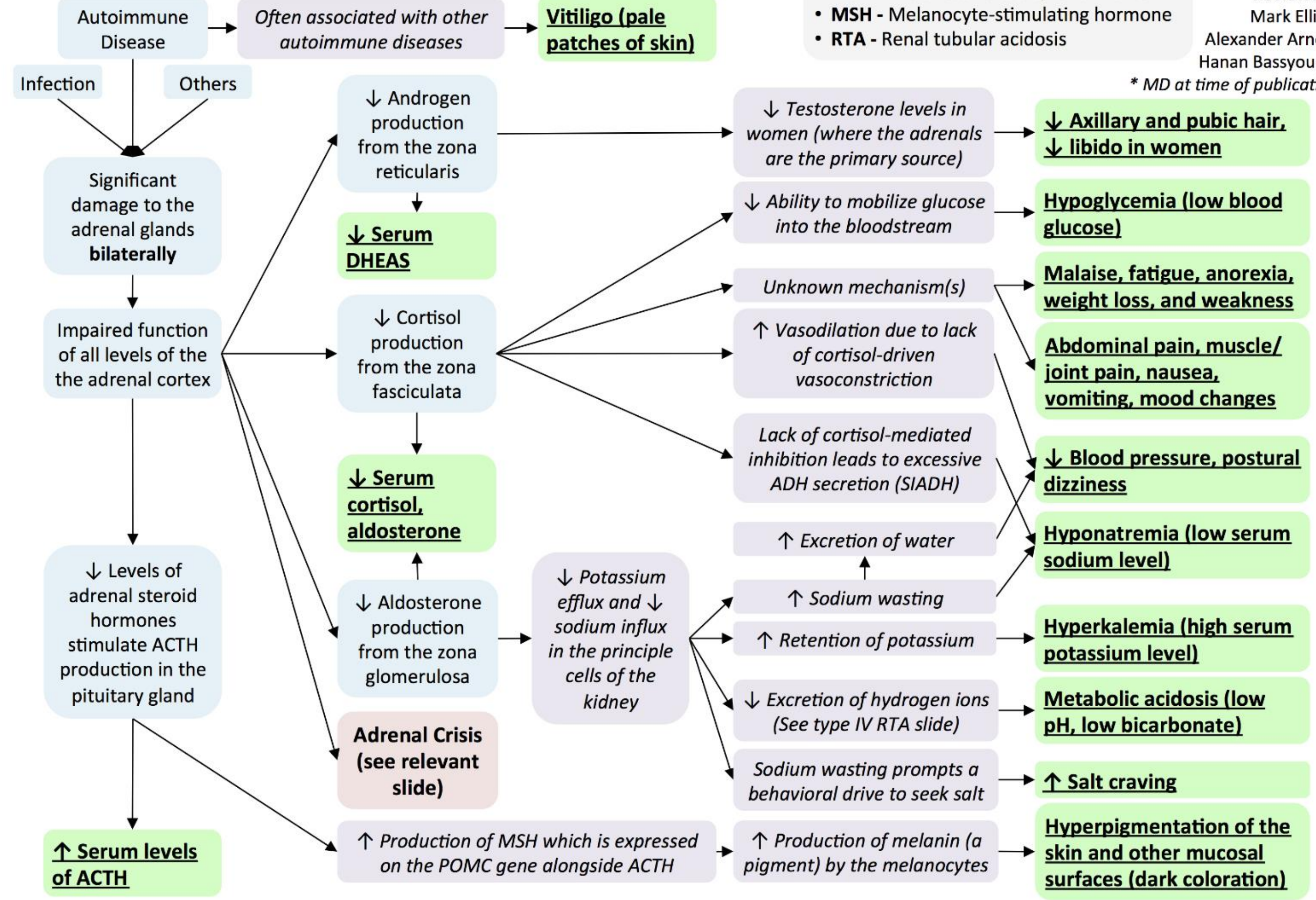

Autoimmune Disease

Often associated with other autoimmune diseases

Vitiligo (pale patches of skin)

Infection

Others

Significant damage to the adrenal glands **bilaterally**

Impaired function of all levels of the the adrenal cortex

↓ Levels of adrenal steroid hormones stimulate ACTH production in the pituitary gland

↑ Serum levels of ACTH

↓ Androgen production from the zona reticularis

↓ Serum DHEAS

↓ Cortisol production from the zona fasciculata

↓ Serum cortisol, aldosterone

↓ Aldosterone production from the zona glomerulosa

Adrenal Crisis (see relevant slide)

↑ Production of MSH which is expressed on the POMC gene alongside ACTH

↓ Potassium efflux and ↓ sodium influx in the principle cells of the kidney

↓ Testosterone levels in women (where the adrenals are the primary source)

↓ Ability to mobilize glucose into the bloodstream

Unknown mechanism(s)

↑ Vasodilation due to lack of cortisol-driven vasoconstriction

Lack of cortisol-mediated inhibition leads to excessive ADH secretion (SIADH)

↑ Excretion of water

↑ Sodium wasting

↑ Retention of potassium

↓ Excretion of hydrogen ions (See type IV RTA slide)

Sodium wasting prompts a behavioral drive to seek salt

↑ Production of melanin (a pigment) by the melanocytes

↓ Axillary and pubic hair, ↓ libido in women

Hypoglycemia (low blood glucose)

Malaise, fatigue, anorexia, weight loss, and weakness

Abdominal pain, muscle/ joint pain, nausea, vomiting, mood changes

↓ Blood pressure, postural dizziness

Hyponatremia (low serum sodium level)

Hyperkalemia (high serum potassium level)

Metabolic acidosis (low pH, low bicarbonate)

↑ Salt craving

Hyperpigmentation of the skin and other mucosal surfaces (dark coloration)

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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21-Hydroxylase Deficiency (21-OHD): *Pathogenesis and clinical findings*

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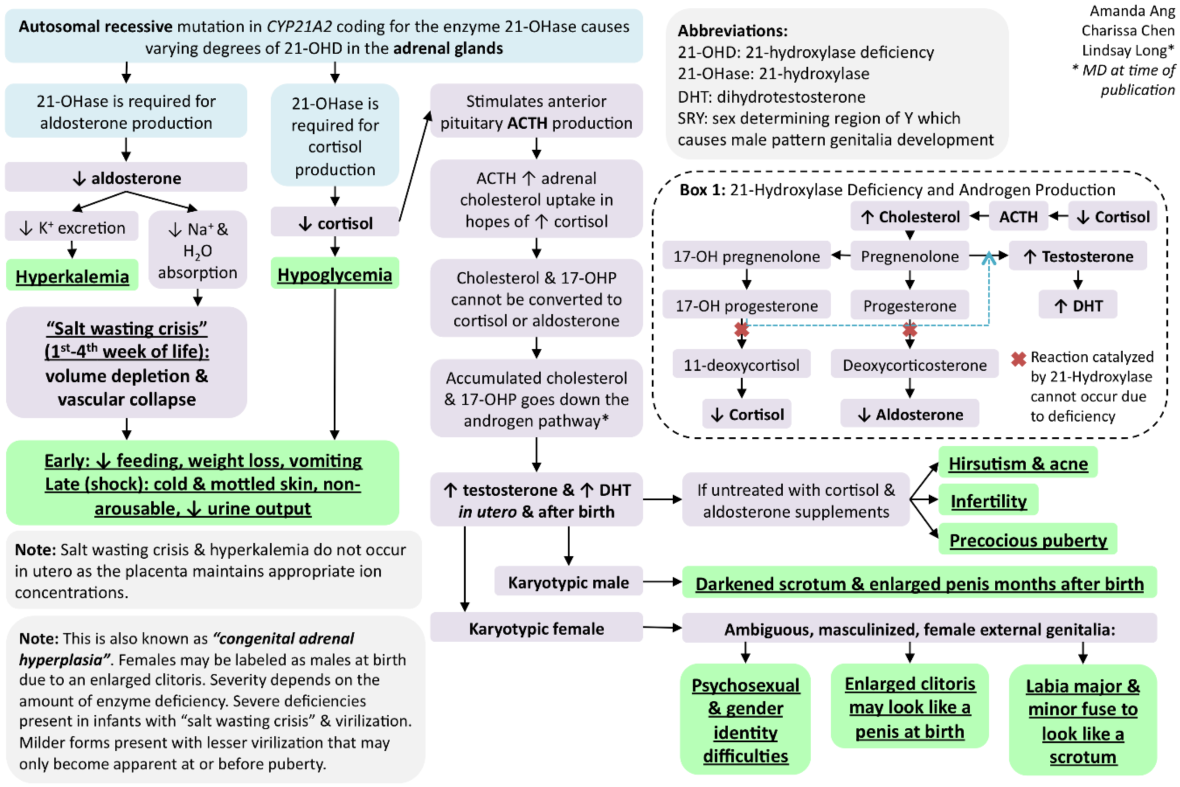
Abbreviations:
21-OHD: 21-hydroxylase deficiency
21-OHase: 21-hydroxylase
DHT: dihydrotestosterone
SRY: sex determining region of Y which causes male pattern genitalia development



Autosomal recessive mutation in *CYP21A2* coding for the enzyme 21-OHase causes varying degrees of 21-OHD in the **adrenal glands**

21-OHase is required for aldosterone production

↓ aldosterone

↓ K^+ excretion

Hyperkalemia

↓ Na^+ & H_2O absorption

"Salt wasting crisis" (1st-4th week of life): volume depletion & vascular collapse

21-OHase is required for cortisol production

↓ cortisol

Hypoglycemia

Early: ↓ feeding, weight loss, vomiting
Late (shock): cold & mottled skin, non-arousable, ↓ urine output

Note: Salt wasting crisis & hyperkalemia do not occur in utero as the placenta maintains appropriate ion concentrations.

Note: This is also known as ***"congenital adrenal hyperplasia"***. Females may be labeled as males at birth due to an enlarged clitoris. Severity depends on the amount of enzyme deficiency. Severe deficiencies present in infants with "salt wasting crisis" & virilization. Milder forms present with lesser virilization that may only become apparent at or before puberty.

Stimulates anterior pituitary **ACTH** production

ACTH ↑ adrenal cholesterol uptake in hopes of ↑ cortisol

Cholesterol & 17-OHP cannot be converted to cortisol or aldosterone

Accumulated cholesterol & 17-OHP goes down the androgen pathway*

↑ testosterone & ↑ DHT *in utero* & after birth

If untreated with cortisol & aldosterone supplements

Hirsutism & acne

Infertility

Precocious puberty

Karyotypic male

Darkened scrotum & enlarged penis months after birth

Karyotypic female

Ambiguous, masculinized, female external genitalia:

Psychosexual & gender identity difficulties

Enlarged clitoris may look like a penis at birth

Labia major & minor fuse to look like a scrotum

Box 1: 21-Hydroxylase Deficiency and Androgen Production

↑ Cholesterol ← **ACTH** ← **↓ Cortisol**

17-OH pregnenolone ← Pregnenolone → **↑ Testosterone** → **↑ DHT**

17-OH pregnenolone → 17-OH progesterone ✖→ 11-deoxycortisol → **↓ Cortisol**

Pregnenolone → Progesterone ✖→ Deoxycorticosterone → **↓ Aldosterone**

✖ Reaction catalyzed by 21-Hydroxylase cannot occur due to deficiency

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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Investigations include:

- Basal cortisol levels (taken in the morning) being low
- Investigating hypoadrenalism usually involves the administration of a synthacen test (synthetic ACTH).
    - In primary adrenal insufficiency (Addison's disease) artificial ACTH will not cause an increase in adrenal hormones
    - In secondary adrenal insufficiency the artificial ACTH will cause an increase in adrenal hormones
- ACTH level testing is also important:
    - ACTH will be increased in a primary adrenal insufficiency
    - ACTH will be decreased in a secondary adrenal insufficiency
- Other tests conducted include FBS, U&E etc.

Treatment includes:

- Glucocorticoid replacement with increased doses for stress and illness
    - This helps to prevent adrenal crisis: in high demand situations people with adrenal insufficiency can enter shock
- Mineralocorticoid replacement
    - This is not usually used in secondary adrenal insufficiency because the zona glomerulosa still responds to RAAS

ANDROGEN DISORDERS

Androgen excess can be caused by gonadal or adrenal disorders. Adrenal causes of androgen excess include:

- Neoplasms
- Congenital adrenal hyperplasia type 1
    - This is a deficiency in 21-hydroxylase enzyme
        - This is responsible for the conversion of 17-hydroxy progesterone into cortisol and aldosterone
        - The result is decreased cortisol levels (leading to increased ACTH expression) which results in increased androgen production
    - Classic 21-hydroxylase deficiency refers to a severe deficiency from prenatal development resulting in prenatal virilisation and intermediate sex characteristics as well as severe dehydration that is life threatening due to aldosterone deficiency.
    - Non-classic 21-hydroxylase deficiency refers to a less severe enzyme deficiency with no evidence at birth by a hyperandrogenism evident after birth
    - Diagnosis is based on clinical features, elevated serum 17-OHP and elevated adrenal androgen levels
- Congenital adrenal hyperplasia type 2
    - This is a deficiency of 11-b hydroxylase enzyme
        - This is responsible for the conversion of 11-deoxycorticosterone into cortisol
        - This causes decreased cortisol levels but does not affect mineralocorticoids as much
    - Classic 11b-hydroxylase deficiency causes prenatal androgen excess, hypertension and the early development of sexual characteristics
    - Non-classic 11b-hydroxylase deficiency causes varying symptoms of hyperandrogenism such as hirsutism and menstrual abnormalities in females and short stature in males due to premature closure of the growth plates

Androgen excess can occur by themselves or in combination with Cushing's disease (owing to the fact that androgen secretion is increased by ACTH)

PITUITARY PATHOLOGY

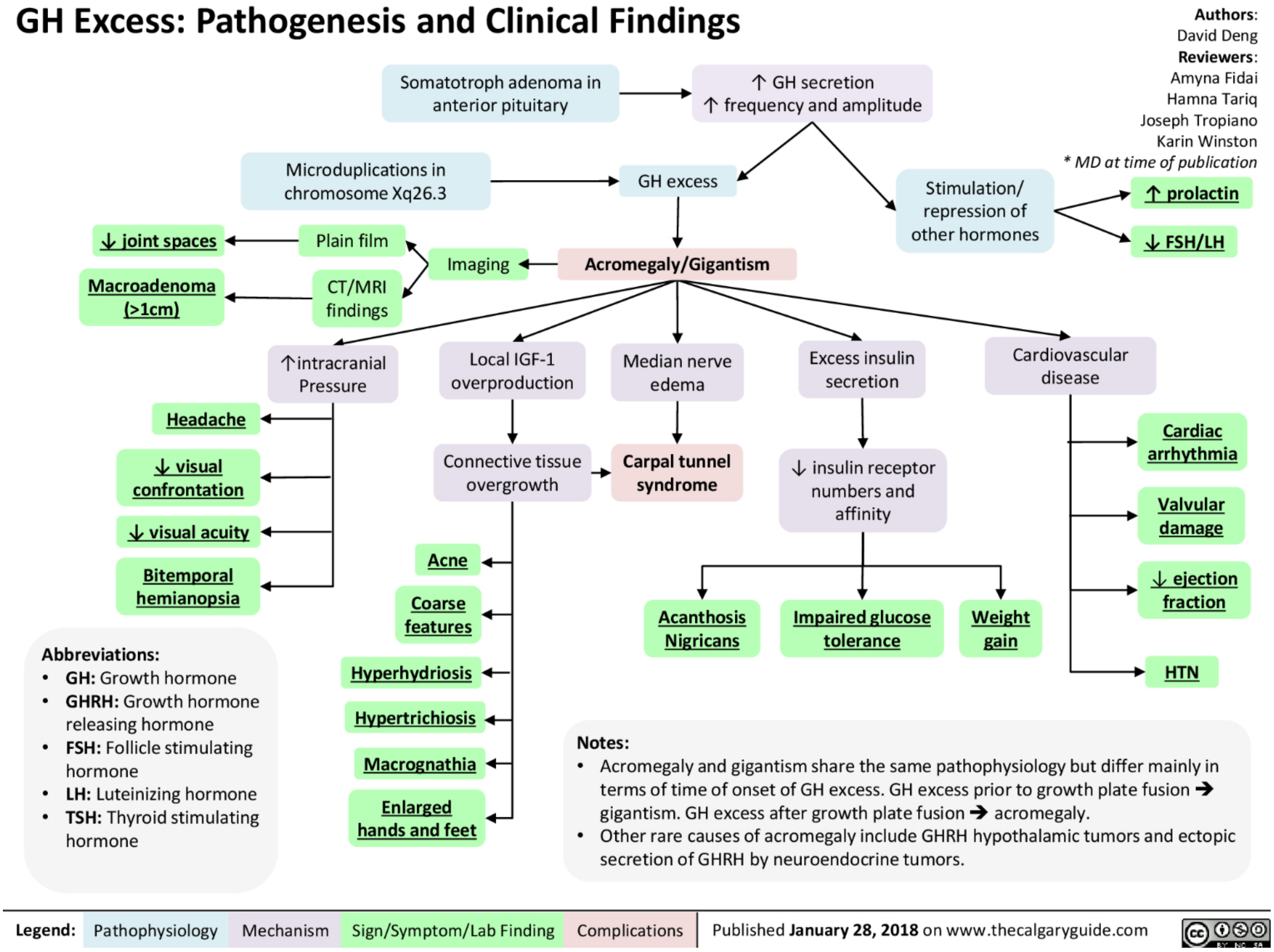
Pituitary hypofunction occurs when over 75% of the gland is absent or destroyed. It can affect one type of cell, multiple types of cells, or all cell types. Causes include:

- Tumours
    - Pituitary adenomas are defined as micro or macro depending on their size as well as on functionality.
        - Prolactinomas affect prolactin secreting cells (this is the most common form of pituitary adenoma)

            - Can cause amenorrhoea, infertility, oestrogen deficiency (because high PRL inhibits GnRH release) and galactorrhea, as well as impotence in men.
            - High PRL may also affect LH release, causing irregular periods.
            - High PRL may also cause decreased ACTH levels which may result in decreased aldosterone and cortisol and associated symptoms (i.e. GIT issues, pain and hyponatremia)
            - Hyperprolactinemia can also be caused by physiological mechanisms as well as by drugs.
            - Investigations of hyperprolactinemia include PRL levels, cortisol levels, visual field examinations, MRIs, pregnancy levels
            - Treatment is indicated in fertility issues as well as when the tumour is of macro size.
                - Dopamine agonists are always used as the first line treatment; dopamine is a natural inhibitor of PRL.
                - Surgery and radiotherapy can be used.
            - Hyperprolactinemia can also be caused by hypothalamic or pituitary disorders that interfere with the secretion of dopamine
        - ACTH secreting cell tumours cause Cushing's disease
        - GH secreting cells cause acromegaly or gigantism
            - If present during childhood will cause gigantism (extreme growth) and if present after childhood will cause acromegaly. Acromegalic features include coarse facial features, enlargement of the hands and feed, impaired glucose tolerance, enlarged heart and jaw, hyperhidrosis, menstrual disturbances. Children whose tumour persists into adulthood can experience both gigantism as well as acromegalic features.
                - Diagnostic features involve demonstrating high IGF-1 levels and a lack of GH suppression following a sugar test (normally GH is inhibited post-sugar)

                - Tumours are usually corrected with surgery, but medication can be used if there is post-surgical high levels of IGF-1 or in poor surgical candidates.

        - TSH causes hyperthyroidism
        - Gonadotropin releasing cell adenomas are usually symptomless
    - The mass effect of tumours can result in sellar manifestations: headaches due to stretching of the dura mater, cranial nerve defects and bitemporal hemianopia. This occurs when there is a visual impairment in the outer edges of both the left and right halves of the visual field.
        - When very serious can also cause CSF rhinorrhoea, hydrocephalus, invasion of the temporal lobes resulting in epilepsy and infarction.
    - These lesions are usually surgically removed using a nasopharyngeal approach through the sphenoid sinus
    - Metastatic cancers can also occur (commonly with breast cancer) as well as other forms of malignant cancer
- Iatrogenic (surgery/radiation)
    - This accounts for up to 95% of causes



GH Excess: Pathogenesis and Clinical Findings

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Somatotroph adenoma in anterior pituitary
↑ GH secretion
↑ frequency and amplitude
Microduplications in chromosome Xq26.3
GH excess
Stimulation/ repression of other hormones
↑ prolactin
↓ FSH/LH
Acromegaly/Gigantism
Imaging
Plain film
↓ joint spaces
CT/MRI findings
Macroadenoma (>1cm)
↑intracranial Pressure
Headache
↓ visual confrontation
↓ visual acuity
Bitemporal hemianopsia
Local IGF-1 overproduction
Connective tissue overgrowth
Acne
Coarse features
Hyperhydriosis
Hypertrichiosis
Macrognathia
Enlarged hands and feet
Median nerve edema
Carpal tunnel syndrome
Excess insulin secretion
↓ insulin receptor numbers and affinity
Acanthosis Nigricans
Impaired glucose tolerance
Weight gain
Cardiovascular disease
Cardiac arrhythmia
Valvular damage
↓ ejection fraction
HTN

Abbreviations:
- **GH:** Growth hormone
- **GHRH:** Growth hormone releasing hormone
- **FSH:** Follicle stimulating hormone
- **LH:** Luteinizing hormone
- **TSH:** Thyroid stimulating hormone

Notes:
- Acromegaly and gigantism share the same pathophysiology but differ mainly in terms of time of onset of GH excess. GH excess prior to growth plate fusion ➔ gigantism. GH excess after growth plate fusion ➔ acromegaly.
- Other rare causes of acromegaly include GHRH hypothalamic tumors and ectopic secretion of GHRH by neuroendocrine tumors.

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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- Pituitary apoplexy
    - Haemorrhage in or impaired blood supply to the pituitary gland causing headache, visual symptoms, altered mental state and hormone dysfunction
- Ischemic necrosis (Sheehan's syndrome)
    - Post-partum hypopituitarism that is a rare complication of haemorrhage and shock in birth associated with reduced blood supply resulting in pituitary necrosis
- Diabetes insipidus
    - Polydipsia and polyuria due to ADH disruption; usually caused by tumour, meningitis, head trauma, SIADH etc. Can also be caused by renal tubule defect resulting in non-responsiveness to ADH.
    - This is tested using a 24-hour urine output test
    - Important to exclude an osmotic diuresis cause by glucose or renal disease
    - Can confirm with standard water deprivation test: individuals with DI will become extremely uncomfortable
    - Partial DI can be treated with maintenance of water balance
- Lymphocytic hypophysistis
    - An autoimmune condition where in the gland becomes infiltrated with lymphocytes causing enlargement and impaired function, most often affecting post-partum or pregnant women
- Hypogonadism can result from decreased FSH and LH secretion as these control testosterone production in men
    - Symptoms include delayed pubertal development, undescended testes, fatigue, irritability, erectile dysfunction, reduced hair growth.

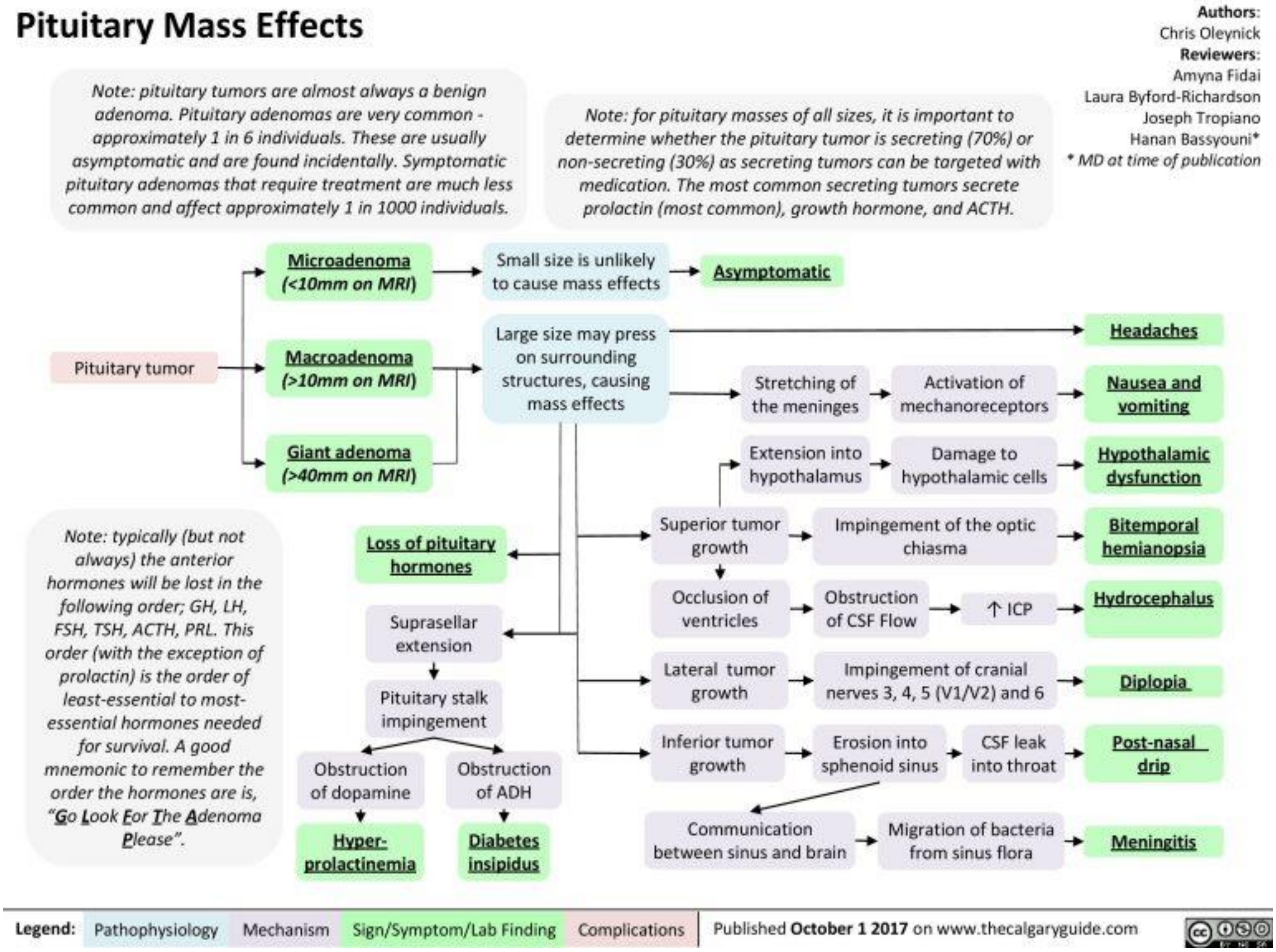
When the pituitary gland fails by itself, the hormones usually develop insufficiency in the following order: GH, LH, FSH, TSH, ACTH.

Diagnosis of complete deficiency is straightforward, whereas dynamic tests are required to detect partial investigations.

- Corticotropic deficiency can be tested using 8am serum cortisol (due to diurnal levels of cortisol), synthacten test, insulin tolerance test.
- Growth hormone deficiency can be tested using insulin tolerance test
- MRI of the pituitary is used

- Visual field testing can be used

Treatment of multiple hypopituitarism involves hormone replacement therapy. Always replace cortisol first, thyroxine next and then the others afterwards.



Pituitary Mass Effects

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Note: pituitary tumors are almost always a benign adenoma. Pituitary adenomas are very common - approximately 1 in 6 individuals. These are usually asymptomatic and are found incidentally. Symptomatic pituitary adenomas that require treatment are much less common and affect approximately 1 in 1000 individuals.

Note: for pituitary masses of all sizes, it is important to determine whether the pituitary tumor is secreting (70%) or non-secreting (30%) as secreting tumors can be targeted with medication. The most common secreting tumors secrete prolactin (most common), growth hormone, and ACTH.

Note: typically (but not always) the anterior hormones will be lost in the following order; GH, LH, FSH, TSH, ACTH, PRL. This order (with the exception of prolactin) is the order of least-essential to most-essential hormones needed for survival. A good mnemonic to remember the order the hormones are is, "Go Look For The Adenoma Please".

Pituitary tumor
Microadenoma (<10mm on MRI)
Macroadenoma (>10mm on MRI)
Giant adenoma (>40mm on MRI)
Small size is unlikely to cause mass effects
Asymptomatic
Large size may press on surrounding structures, causing mass effects
Headaches
Stretching of the meninges
Activation of mechanoreceptors
Nausea and vomiting
Extension into hypothalamus
Damage to hypothalamic cells
Hypothalamic dysfunction
Superior tumor growth
Impingement of the optic chiasma
Bitemporal hemianopsia
Occlusion of ventricles
Obstruction of CSF Flow
↑ ICP
Hydrocephalus
Lateral tumor growth
Impingement of cranial nerves 3, 4, 5 (V1/V2) and 6
Diplopia
Inferior tumor growth
Erosion into sphenoid sinus
CSF leak into throat
Post-nasal drip
Communication between sinus and brain
Migration of bacteria from sinus flora
Meningitis
Loss of pituitary hormones
Suprasellar extension
Pituitary stalk impingement
Obstruction of dopamine
Obstruction of ADH
Hyper-prolactinemia
Diabetes insipidus

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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FEMALE REPRODUCTIVE PATHOLOGY

Female reproductive pathology can usually be broken down into the causes of major symptomatology. These include:

Menstrual disturbance:

- Menorrhagia
- Oligomenorrhoea
- Amenorrhea
    - Primary: never before had a period
    - Secondary: previous period normal followed by loss of period
- Intermenstrual bleeding
    - May be caused by ovulatory defect due to a luteal phase defect
    - May be caused by anovulation resulting in lack of progesterone surge and prolonged oestrogen

Abnormal bleeding:

- Post-coital bleeding
- Post-menopausal bleeding

Pelvic masses:

- Ovarian mass
- Uterine/cervical mass
- Vaginal mass

Pelvic pain:

- Acute
    - May be caused by endometritis or inflammation of the endometrium. This can be acute as well as chronic. Acute endometritis is associated with fevers and can be associated with retained products of conception of the placenta. Chronic endometritis can be associated with low-grade chronic infection. Acute endometritis will feature neutrophils in the tissue, while chronic will feature plasma cells.
- Chronic
    - Dysmenorrhea
    - Dyspareunia

Lower genital symptoms:

- Vaginal discharge
- Lesions

- Vulvodynia

AMENORRHOEA:

Amenorrhea is the absence of a period. It is counted from the length of the last period.
Oligomenorrhea is the state of having menstrual periods >35 days apart or less than 9 periods per year.
Primary amenorrhoea can be caused by:

- Chronic illness
- Functional hypothalamic amenorrhoea
- Iatrogenic
- Congenital hypopituitarism
- Tumours
- Turner syndrome
- Gonadal dysgenesis
- POI
- Vaginal agenesis
- Intersex disorders
- Pregnancy
- PCOS
- Addison's disease
- Cushing's syndrome
- Thyroid disease

Secondary amenorrhea can be caused by:

- Functional hypothalamic amenorrhea
- Chronic illness
- Tumours (particularly prolactinoma)
- Hyperprolactinemia of any cause
- POI
- Radiation
- Chemotherapy
- Pregnancy
- PCOD
- Contraceptive use
- Thyroid disease
- Congenital adrenal hyperplasia

Functional hypothalamic amenorrhea occurs when there is abnormal GnRH secretion and decreased gonadotropin pulsation. It may be because of lower leptin levels that the GnRH secretion is reduced. This results in the absence of a physiological LH surge, low oestrogen levels and normal FSH levels. It can be caused by anorexia nervosa, exercise, extreme diets and stress.

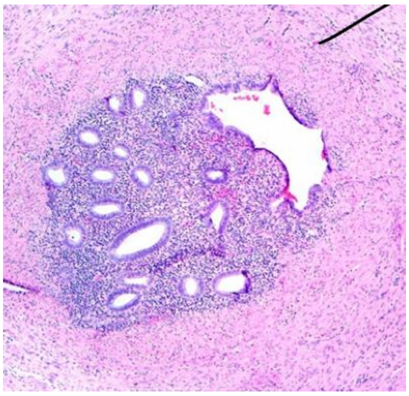
- This can sometimes be seen in the athletic triad: amenorrhoea, disordered eating and osteoporosis

Turner syndrome is a genetic chromosomal condition resulting in oocytes and follicles undergoing apoptosis. The ovaries are replaced with fibrous tissue and no ovarian oestrogen secretion occurs.
POI occurs when there is the development of clinical menopause symptoms prior to the age of 40 in women with no other cause. This usually causes secondary amenorrhoea.

ENDOMETRIOSIS:

Endometriosis refers to the presence of endometrial tissue in an extra-uterine position. Common locations include the ovary or peritoneum but can occur anywhere in the body. The tissue undergoes normal proliferation and shedding with the menstrual cycle, causing the lesions to enlarge and become haemorrhagic resulting in irritation, pain and abnormal bleeding. It affects between 2-10% of all women of reproductive age. The cause of endometriosis is unknown but there are multiple theories.
Symptoms include:

- Infertility
    - Infertility can occur because the endometrial tissue can cause scarring and fibrous adhesions that can alter the normal reproductive anatomy (i.e. adhesions of the fallopian tubes etc).
- Dysmenorrhea
- Dyspareunia
- Chronic pelvic pain
- Pain on defecation
- Can be asymptomatic



The endometrial implants are often present as macroscopically visible yellow-brown spots or islands of tissue on the surface of other tissues or organs. The brown-black colour is caused by bleeding and blood breakdown products. The endometrial tissue can include both glandular and stromal tissue, but only stroma is needed for diagnosis.
Chocolate cysts are large cysts of endometrial tissue that form on the ovary, taking on a dark brown colour giving them their name.
Theories of aetiology include:

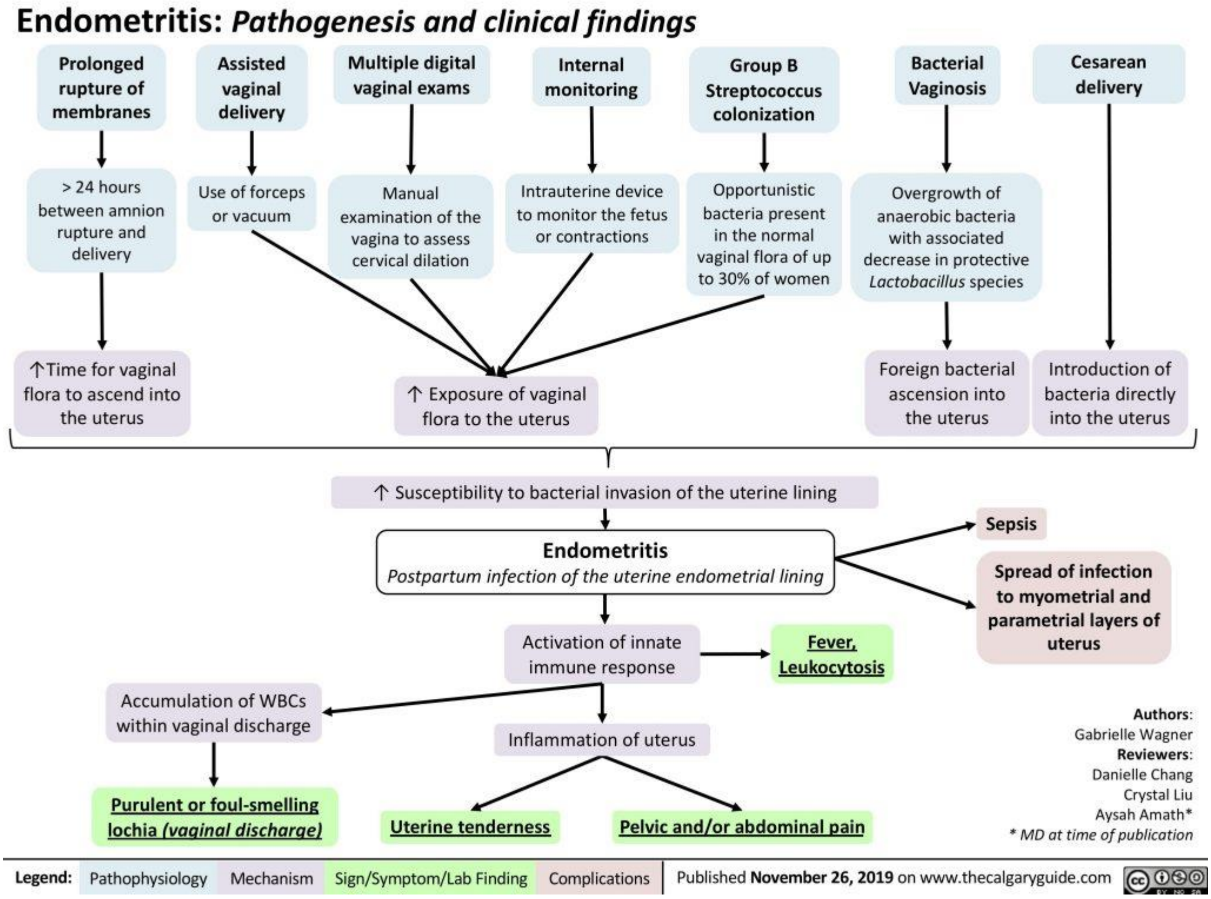
- Regurgitation theory: blood is regurgitated backwards through the fallopian tube and into the pelvis during the menstrual cycle, causing tissue to grow elsewhere.
    - This occurs in >90% of normal periods but does not always result in endometriosis
- Benign metastasis theory: endometrial tissue spreads via the lymphatic system to distant sites

- Metaplastic theory: the endometrium directly arises from the mesothelial tissue of the abdomen and pelvis during embryogenesis

Treatment of endometriosis includes:

- Analgesics (of limited benefit)
- Androgens, progestins, continuous GnRH administration
- Aromatase inhibitors
- Laser ablation of lesions

Adenomyosis is the name given to the presence of normal endometrial glands within the myometrial tissue. Because the myometrium and endometrium are not always clearly demarcated, they need to be relatively deep within the tissue (2.5cm).


Endometritis: Pathogenesis and clinical findings
Prolonged rupture of membranes
Assisted vaginal delivery
Multiple digital vaginal exams
Internal monitoring
Group B Streptococcus colonization
Bacterial Vaginosis
Cesarean delivery
> 24 hours between amnion rupture and delivery
Use of forceps or vacuum
Manual examination of the vagina to assess cervical dilation
Intrauterine device to monitor the fetus or contractions
Opportunistic bacteria present in the normal vaginal flora of up to 30% of women
Overgrowth of anaerobic bacteria with associated decrease in protective Lactobacillus species
↑Time for vaginal flora to ascend into the uterus
↑ Exposure of vaginal flora to the uterus
Foreign bacterial ascension into the uterus
Introduction of bacteria directly into the uterus
↑ Susceptibility to bacterial invasion of the uterine lining
Endometritis
Postpartum infection of the uterine endometrial lining
Sepsis
Spread of infection to myometrial and parametrial layers of uterus
Activation of innate immune response
Fever, Leukocytosis
Accumulation of WBCs within vaginal discharge
Inflammation of uterus
Purulent or foul-smelling lochia (vaginal discharge)
Uterine tenderness
Pelvic and/or abdominal pain
Authors:
Gabrielle Wagner
Reviewers:
Danielle Chang
Crystal Liu
Aysah Amath*
* MD at time of publication
Legend: Pathophysiology Mechanism Sign/Symptom/Lab Finding Complications
Published November 26, 2019 on www.thecalgaryguide.com

LEIOMYOMA:

This is a well circumscribed benign tumour of smooth muscle that can occur throughout the reproductive tract. They are commonly known as fibroids. This is an extremely common condition. They can be classified as:

- Subserosal: on the tissue surface
  - These can be pedunculated
  - These often only have mass effect symptoms
- Intramural: within the wall of the tissue
- Submucosal: inside of the organ tissue cavity
  - Most likely to cause increased bleeding

They are benign but can cause complications such as haemorrhage, degeneration, torsion (for pedunculated fibroids), menorrhagia and mass effect.

- They themselves do not bleed but increase the surface area of the endometrium thus promoting hypervascularity

Depending on the location the mass effect can cause uterine and/or bladder symptoms due to compression or obstruction. Their mass effect may also cause infertility and bleeding may result in iron deficiency anaemia. They may also sometimes be asymptomatic.

Symptomatic fibroids require treatment, while asymptomatic fibroids usually do not need treatment. If no treatment is given, frequent follow ups are necessary to monitor growth and symptoms.

- Hormone therapy can be used to prevent growth (usually GnRH agonists) as these decrease tumour vascularisation and decrease leiomyoma zine
- Embolization of the fibroid can be used (injection of PVA into the arteries supplying the fibroid) to decrease size
- Surgical therapy is indicated when the tissue is rapidly growing, causing severe bleeding or other symptoms.

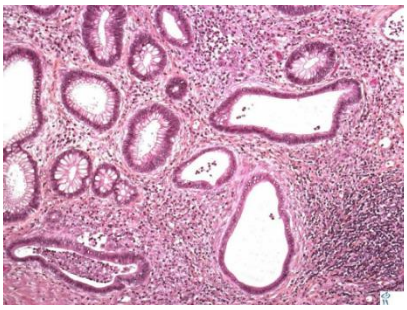
Recurrence of fibroids is common. There is also an increased risk of breech presentation, prematurity and miscarriage in pregnancy women.

Fibroids will normally naturally shrink post-menopause because of the fall in oestrogen levels.

ENDOMETRIAL POLYPS:

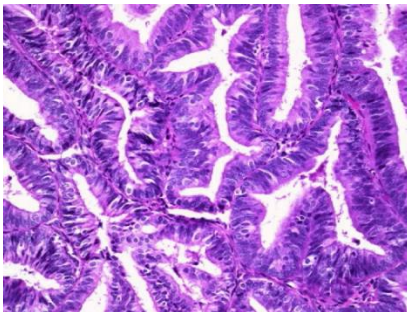
These are polypoid lesions of the endometrium that involve proliferation of glands and/or stroma. They can be both asymptomatic or may cause menorrhagia, irregular bleeding, post-menopausal bleeding, infertility and pain. They are usually oestrogen-dependant. They can be both benign and malignant but are more commonly benign.

They are associated with menopause, obesity, hypertension and tamoxifen use. They are usually small enough to not cause uterine enlargement.



They are investigated with ultrasound, cervical cell cytology and biopsy.
They have a histological appearance that shows distorted and wide-lumened glands. They are widely spaced with lots of intervening stroma, unlike normal endometrial tissue.
They can be both observed with regular imaging or excision.

ENDOMETRIAL HYPERPLASIA

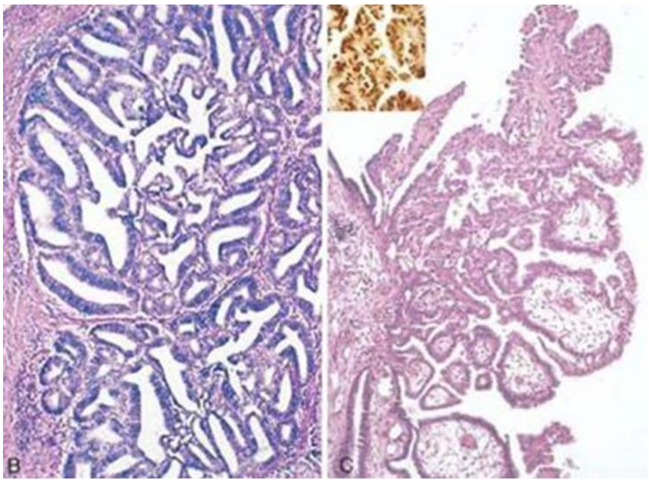


This is an abnormal thickening of the endometrium that occurs both idiopathically as well as with the presence of excess or unopposed oestrogen release. This may occur in patients with PCOS, hormone replacement therapy or estrogen-producing tumours.
The endometrial architecture is disturbed, and the glands become more complex and closely packed. The complexity of the glands can be best seen in the in-folding of the glands. There is basically an absence of stromal tissue between the glands.
Endometrial hyperplasia is defined as either having simple or complex architecture and may or may not have cytological atypia such as nuclear enlargement, hyperchromicity etc. Complex type hyperplasia causes a higher risk of cancer than simple hyperplasia.
Endometrial hyperplasia is associated with an increased risk of type I endometrial adenocarcinoma.
Symptoms of endometrial hyperplasia include constant or intermenstrual bleeding.
Treatment is usually progesterone suppression, but hysterectomy may be used in women with no desire to conceive to prevent the change of cancer.

ENDOMETRIAL ADENOCARCINOMA

There are two main types of endometrial adenocarcinoma. These are:

- Endometrioid/Type I: have a glandular tissue appearance with increased crowding and cribriform appearance of glands, decreased stroma, increased proliferation and mitoses.
    - Usually has an endometrial hyperplasia precursor
    - More common; most common malignancy of the female reproductive tract
    - Occur due to unopposed oestrogen stimulation, obesity
    - Common mutations include PTEN, K-Ras
    - Associated with nulla gravid, early menarche and late menopause
        - These things all increase oestrogen exposure and cycle number
    - Can be divided into grade 1-3 depending on the degree of cellular differentiation seen
    - Can be staged based on depth of myometrial invasion and metastasis
    - Usually diagnosed early and have a 95% relapse free survival rate when treated
- Serous/Type II: have a papillary appearance
    - Usually no endometrial hyperplasia precursor
    - Oestrogen independent
    - Occur in older women
    - Associated with a p53 mutation and associated with genetic predisposition
    - Metastases to the cervix, vagina, ovaries and ovarian tubes are common
    - Prognosis is positive if diagnosed prior to metastasis, but usually detected after this
    - Often recurs with tumour spear
    - These are associated with invasion, necrosis, poor differentiation on histology



Symptoms:

- Abnormal uterine bleeding is the most common symptom (includes post-menopausal bleeding) for type I endometrioid cancers
    - Does not occur in serous type II cancers
- Pelvic pain, abdominal masses and/or weight loss

Treatment:

- Progesterone therapy is possible for low grade and early stage type I cancers
- Hysterectomy can be used for more aggressive cancers

PELVIC INFLAMMATORY DISEASE

This is an infection of the upper genital tract that can occur as a result of both a sexually transmitted infection or post-instrumentation as well as post-conception or pregnancy if products are retained. Chronic inflammation can lead to fibrosis and scarring of the reproductive tract with adhesions which can result in infertility.
This is usually caused by:

- Chlamydia
- Gonorrhoea

Symptoms include:

- Chronic pain
- PV discharge
- Infertility

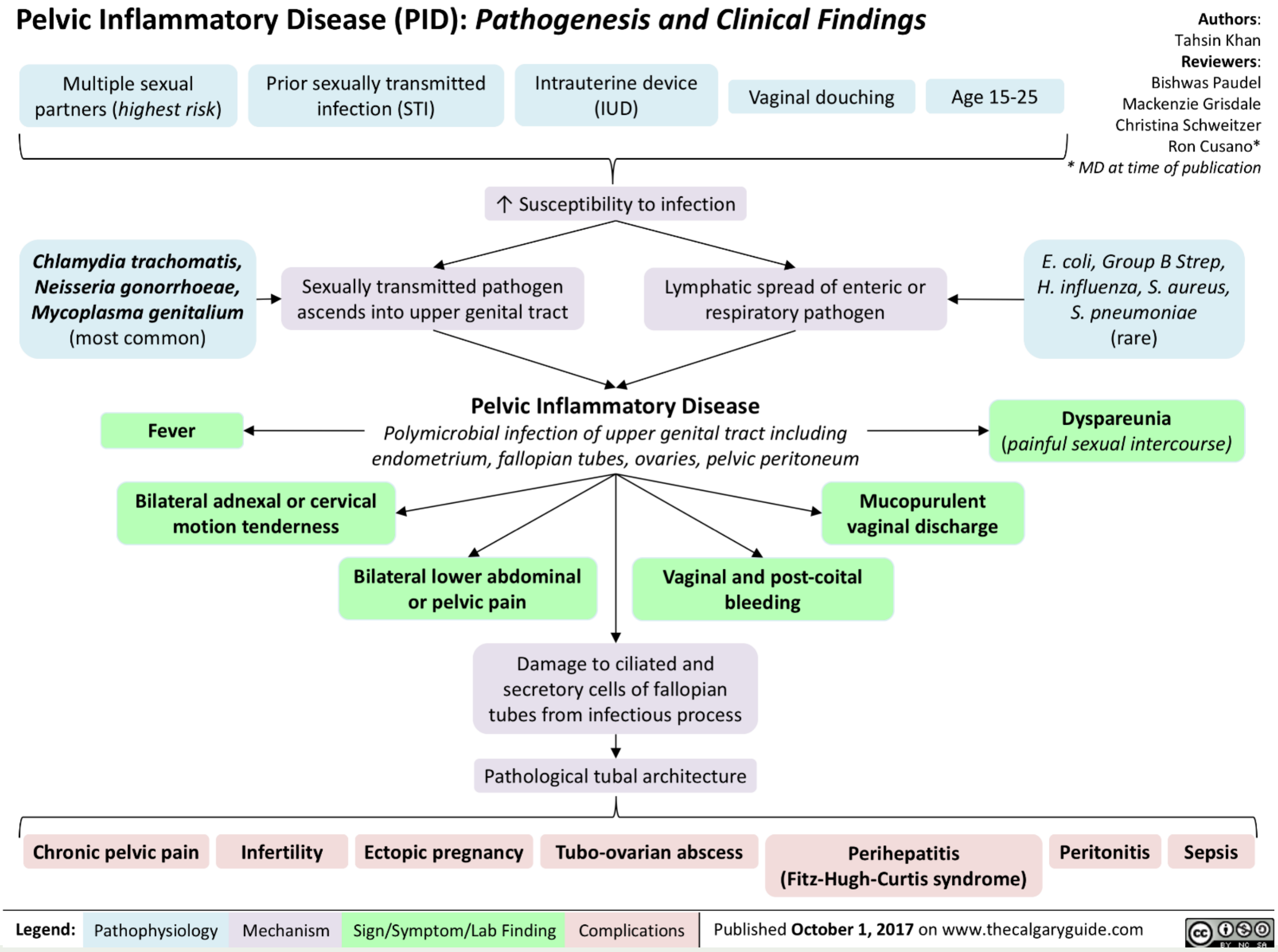
Complications include:

- Pyosalpinx: dilated and pus-filled ovarian tube

- Peritonitis
- Tubo-ovarian adhesions: torsion, hydrosalpinx, ectopic pregnancy
    - Hydrosalpinx occurs when the ovarian tube is filled with fluid and becomes dilated
- Infertility
    - Due to adhesions and altered anatomy

PID should be investigated via hysterosalpingogram.

Treatment involves appropriate antibiotics.



Pelvic Inflammatory Disease (PID): *Pathogenesis and Clinical Findings*

Authors:
Tahsin Khan
Reviewers:
Bishwas Paudel
Mackenzie Grisdale
Christina Schweitzer
Ron Cusano*
** MD at time of publication*

Multiple sexual partners (*highest risk*)

Prior sexually transmitted infection (STI)

Intrauterine device (IUD)

Vaginal douching

Age 15-25

↑ Susceptibility to infection

Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium (most common)

Sexually transmitted pathogen ascends into upper genital tract

Lymphatic spread of enteric or respiratory pathogen

E. coli, Group B Strep, H. influenza, S. aureus, S. pneumoniae (rare)

Pelvic Inflammatory Disease
Polymicrobial infection of upper genital tract including endometrium, fallopian tubes, ovaries, pelvic peritoneum

Fever

Dyspareunia *(painful sexual intercourse)*

Bilateral adnexal or cervical motion tenderness

Mucopurulent vaginal discharge

Bilateral lower abdominal or pelvic pain

Vaginal and post-coital bleeding

Damage to ciliated and secretory cells of fallopian tubes from infectious process

Pathological tubal architecture

Chronic pelvic pain

Infertility

Ectopic pregnancy

Tubo-ovarian abscess

Perihepatitis (Fitz-Hugh-Curtis syndrome)

Peritonitis

Sepsis

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

Published **October 1, 2017** on www.thecalgaryguide.com

POLYCYSTIC OVARIAN SYNDROME

Normal cysts are common on the ovaries – the appearance of normal follicles is very cyst-like.

PCOS is the most common endocrinopathy in women, affecting between 8-13%. It is characterised by hyperandrogenism and anovulation. It is a very variable syndrome characterised by the following:

- Androgen excess
    - Produced by ovarian theca cells (causes thecal cell hyperplasia)
- Oligomenorrhoea
    - Due to disruption of LH/FSH balance resulting in impaired follicle maturation
- Hirsutism
- Obesity
- Infertility or subfertility
- Lower abdominal pain
- Acne
- Alopecia
    - Due to androgen excess
- Hyperlipidaemia
- Insulin resistance and hyperinsulinemia

Although insulin resistance is not required for diagnosis, up to 50% of patients have metabolic disease. This means patients with PCOS are at a higher risk of cardiovascular disease. Unopposed estrogen effects (because of lack of ovulation) also results in increased risk of endometrial hyperplasia and endometrial adenocarcinoma.

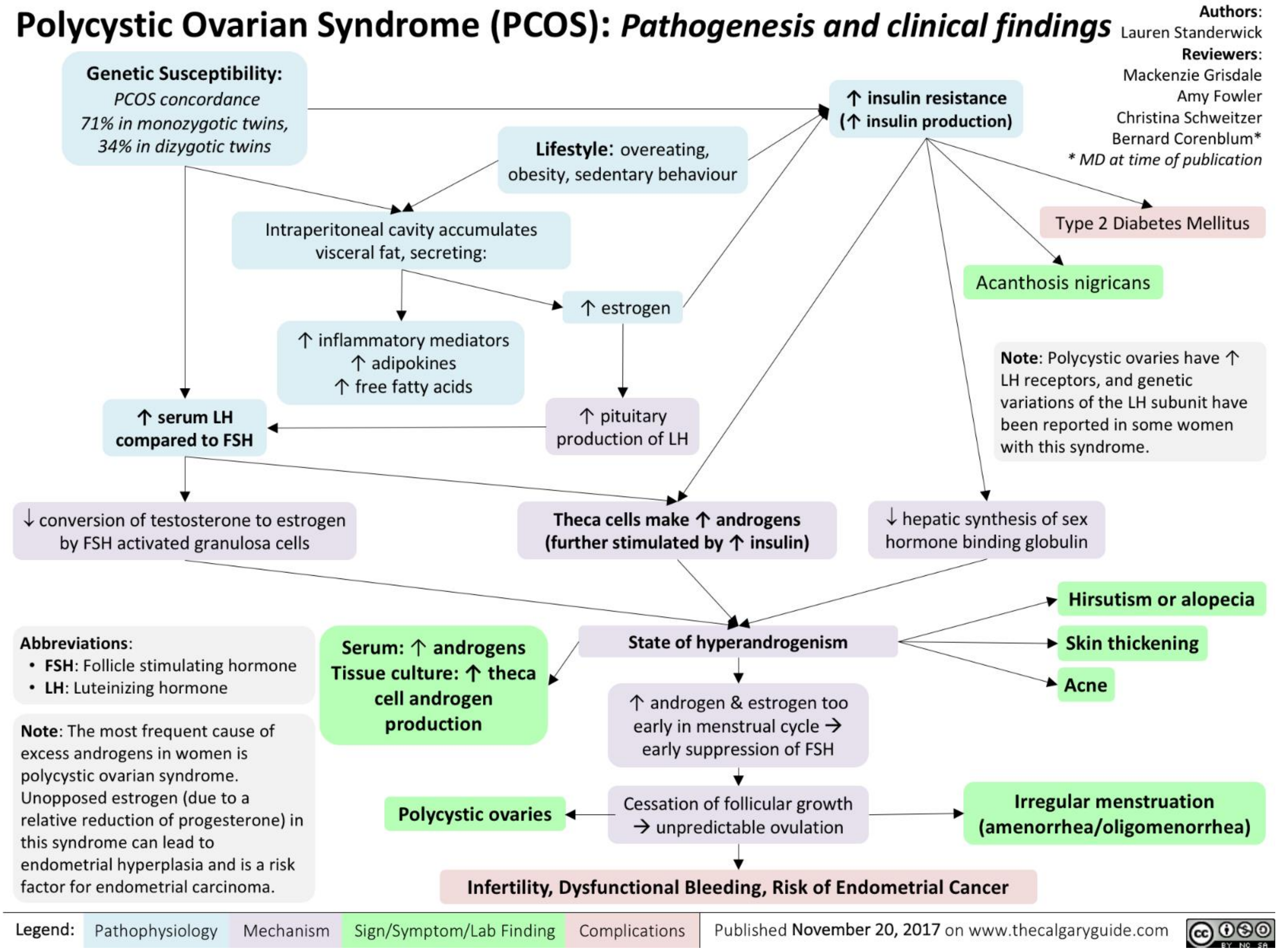
For diagnosis to be made, the female must exhibit 2 of the 3 following symptoms along with exclusion of other aetiology:

1. Ovulatory dysfunction (oligo- or anovulation)
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovarian morphology on ultrasound
    a. Tend to have enlarged ovaries with increased number of follicles
        i. Follicle number per ovary is >20 and or/ ovarian volume >10mL

        - ii. Only one polycystic ovary is required
    - b. Not all polycystic ovaries are symptomatic of PCOS

On histology the ovaries will have:

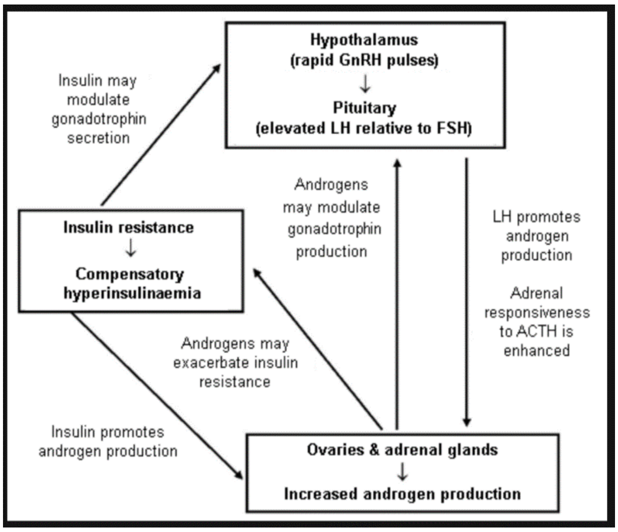
- Absent corpus luteum
- Capsular thickening
- Bilaterally enlarged
- Subcapsular follicles
- Thecal cell hyperplasia


Polycystic Ovarian Syndrome (PCOS): Pathogenesis and clinical findings
Authors: Lauren Standerwick
Reviewers: Mackenzie Grisdale, Amy Fowler, Christina Schweitzer, Bernard Corenblum*
* MD at time of publication
Genetic Susceptibility: PCOS concordance 71% in monozygotic twins, 34% in dizygotic twins
Lifestyle: overeating, obesity, sedentary behaviour
↑ insulin resistance (↑ insulin production)
Type 2 Diabetes Mellitus
Acanthosis nigricans
Intraperitoneal cavity accumulates visceral fat, secreting:
↑ inflammatory mediators ↑ adipokines ↑ free fatty acids
↑ estrogen
↑ pituitary production of LH
↑ serum LH compared to FSH
Note: Polycystic ovaries have ↑ LH receptors, and genetic variations of the LH subunit have been reported in some women with this syndrome.
↓ conversion of testosterone to estrogen by FSH activated granulosa cells
Theca cells make ↑ androgens (further stimulated by ↑ insulin)
↓ hepatic synthesis of sex hormone binding globulin
State of hyperandrogenism
Hirsutism or alopecia
Skin thickening
Acne
Abbreviations:
• FSH: Follicle stimulating hormone
• LH: Luteinizing hormone
Serum: ↑ androgens Tissue culture: ↑ theca cell androgen production
↑ androgen & estrogen too early in menstrual cycle → early suppression of FSH
Note: The most frequent cause of excess androgens in women is polycystic ovarian syndrome. Unopposed estrogen (due to a relative reduction of progesterone) in this syndrome can lead to endometrial hyperplasia and is a risk factor for endometrial carcinoma.
Polycystic ovaries
Cessation of follicular growth → unpredictable ovulation
Irregular menstruation (amenorrhea/oligomenorrhea)
Infertility, Dysfunctional Bleeding, Risk of Endometrial Cancer
Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications
Published November 20, 2017 on www.thecalgaryguide.com

Potential complications of PCOS include CVD and related events, the development of type 2 diabetes, endometrial cancer and a heightened miscarriage rate.

Treatment of PCOS will differ depending on whether the patient is seeking to conceive or not. For all patients, reduction in weight and lifestyle changes to improve insulin resistance are encouraged. This is most important in overweight patients.

- For patients not looking to conceive, the combined OCP is used as treatment
    - This helps abnormal bleeding as well as having anti-adrenergic effects
- For patients seeking to conceive, ovulation induction is attempting with either drugs or laparoscopic ovarian drilling


Hypothalamus (rapid GnRH pulses)
↓
Pituitary (elevated LH relative to FSH)
Insulin may modulate gonadotrophin secretion
Androgens may modulate gonadotrophin production
LH promotes androgen production
Adrenal responsiveness to ACTH is enhanced
Insulin resistance
↓
Compensatory hyperinsulinaemia
Androgens may exacerbate insulin resistance
Insulin promotes androgen production
Ovaries & adrenal glands
↓
Increased androgen production

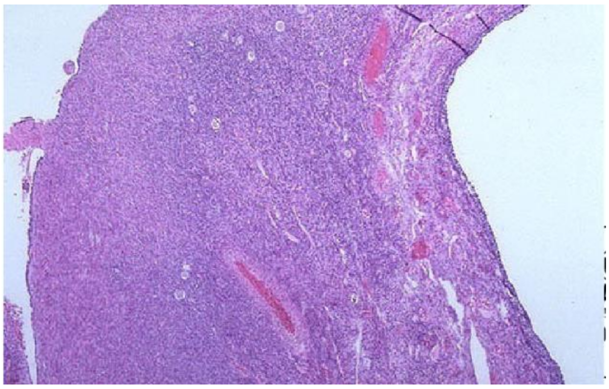
OVARIAN TUMOURS

Ovarian tumours (when malignant) are the most lethal of all female reproductive tumours because they are often detected later than others due to the asymptomatic nature. They can be both primary, arising from the normal ovarian structures, or secondary, involve metastasis from other cancers. Bilateral ovarian cancers are more common caused by secondary metastases.

General symptoms include chronic pain, dyspareunia, acute pain due to bleeding, torsion or rupture or PV bleeding. Changes to bladder or bowel habit, increased feelings of fullness and bloating may also be common.

Primary ovarian neoplasms include:

- Epithelial ovarian cystadenomas (benign)
- Epithelial ovarian carcinoma
    - These are most common ovarian tumours and they arise from the surface epithelium of the ovary and/or the ovarian tube
        - They are usually diagnosed late as they are notoriously asymptomatic. Symptoms may include:



            - Bloating
            - Distention
            - Pain
            - Changes in bowel or bladder function
    - They can be subtypes based on their histological appearance into:
        - Serous: divided into two types depending on their causative mutations
            - Low grade type 1
            - Low grade type 2 (more likely arise from the ovarian tubes)
        - Mucinous
            - Appear like GIT tissue; should always exclude GI metastasis
        - Endometrioid
            - May be related to endometriosis
            - Associated with OCP use and decreased parity
        - Clear cell
        - Other
    - Their malignant potential is based on cytological atypia and architectural complexity and invasion.
    - Risk factors include nulliparity, early menarche, late menopause, oestrogen hormone replacement therapy or other causes of increased oestrogen levels, smoking and obesity
    - There is no effective screening test for ovarian cancer
- Stromal tumours
- Teratoma
- Germ-cell tumours
    - Teratomas: keratinous debris often with evidence of other tissue types
    - Dysgerminoma
    - Yolk-sac tumours
    - Choriocarcinoma

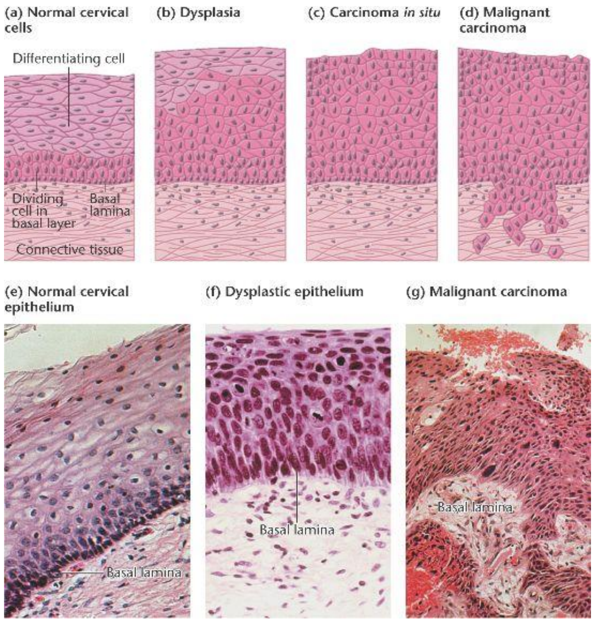
FEMALE INFERTILITY:

Major causes include:

- Anovulation:
    - Hypothalamic dysfunction
        - Stress
        - Overexercise / weight loss
        - Severe illness
        - Hyper/hypothyroidism
    - Pituitary dysfunction\
        - Prolactinoma
    - Ovarian failure
        - Turner's syndrome
        - Fragile X carrier
        - Autoimmune disease
        - Chemo/radiotherapy
- Pelvic disease
    - Tubal disease
        - PID most important – reduced tubal patency
        - Ruptured appendicitis or peritonitis
    - Intrauterine adhesions
        - Curettage
        - Infection
        - Recent pregnancy
    - Endometriosis

CERVICAL CANCER

The endocervix is lined by glandular epithelium, while the ectocervix is lined by squamous epithelium. This means that the endocervix experiences adenocarcinoma and the ectocervix experiences carcinoma. There are varying grades and degrees of cervical neoplasia, ranging from dysplasia through to invasive cancer. Cancers of the lower genital tract in females are almost exclusively caused by HPV types 16 and 18.
Mortality and incidence rates for cervical cancer have drastically fallen after the introduction of the HPV vaccine.
There are two systems for classification of cervical cancer: the Bethesda system which looks at smears, and the histological SIL or CIL terminology which looks at biopsies of the tissue. The Bethesda system is 2 tiered, counting the smears as either low grade or high grade squamous intraepithelial lesions, while the CIN system is 3 tiered and considers CIN1, CIN2 and CIN3 as mild, moderate and severe dysplasia.



- CIN1 refers to neoplastic changes on the bottom levels of the epithelium with retained architecture
    - Neoplastic changes often refer to increased mitotic figures and loss of polarity (this refers to all CIN stages)
    - Koilocytes may be present
        - Koilocytes are characterised by well-defined, clear, balloon like halo around the nucleus and hyperchromicity
- CIN2 refers to more than 2/3 of the epithelium involved, with smaller cell sizes causing increased nuclear to cytoplasmic ratio
- CIN3 refers to the whole epithelial layer involvement and an increased nuclear to cytoplasmic ratio

80% of cervical cancer is cervical squamous cell carcinoma
- These feature irregular cell morphology, hyperchromatic cells with abnormally shaped nuclei, increased mitotic activity, prominent nucleoli and a loss of the basal membrane of the epithelial layer

15% is cervical adenocarcinoma
- This features atypical columnar epithelium with a changed architecture and elongated nuclei

Risk factors for cervical cancer development include:
- Early onset of sexual activity
- Smoking
- Not having had the HPV vaccine
- High parity
- Oral contraceptive use

Clinical features of cervical cancer include:
- Abnormal vaginal bleeding and discharge
- Cervical ulceration
- Symptoms of tumour metastasis (commonly to the vagina, bladder and rectum)

Diagnosis of cervical cancer involves the cervical smear. This involves collection of a specimen from the cervical tissue for microscopic investigation. Standard HPV screening involves a CST every 5 years past the age of 25, and positive HPV tests indicate the need for further investigation. Colposcopy allows for a closer visualisation and biopsy.

Treatment of cervical cancers is directed by the stage and severity of the cancer.
- Low grade cancers are excised with recurrent follow up
- Minimally invasive disease is often treated with excision but can also be treated with hysterectomy
- Advanced cancers are addressed using chemotherapy, radiation and surgery unless contraindicated

Prognosis for non-invasive or minimally invasive disease is very good.

LICHEN SCLEROSIS

This is a chronic inflammatory condition that primarily affects the vulva of the vagina. It causes smooth white plaques to form that can fuse to form scarring. It is most commonly seen in post-menopausal women. This can result in atrophy and distortion over time, which results in a narrowing of the vaginal opening or introitus.
- On histology the lesions will show an atrophic and thin epidermis, a thinned and scarred dermis and chronic inflammatory cell presence in the dermis
    - The earlier the stage of the condition, the higher in the dermis the inflammatory cells will be
    - Scarring in histology is indicated by pale and acellular tissue

The conditions can be scaly, itchy and painful for patients.

It is not a malignant cancer but increases the risk of developing squamous cell carcinoma in the future.

INFLAMMATORY BREAST CONDITIONS

Mastitis:
- Lactational mastitis is a common condition that present in pregnancy. Symptoms include:
    - Swollen, sore, red and tender breasts
    - Systemic signs of infection (fever, fatigue etc)
- This is treated with antibiotic course
    - Only antibiotics safe for use in lactation should be used
- Women are told to continue breastfeeding during mastitis
    - Further milk stasis can aggravate tenderness
- Mastitis can develop into an abscess which can be surgically drained with ultrasound guidance
- Histologically will appear as dense neutrophil infiltrate with occasional multinucleated giant cells
- Non-lactational mastitis occurs when there is a chronic inflammation of the breast tissue and can be divided into:
    - Periductal: related to smoking and fibrocystic change
        - Inflammatory cells will be centred around a duct
    - Granulomatous: usually idiopathic but may be caused by granuloma-forming infection
        - Granulomas will be present in the breast tissue
    - Lymphocytic: found in diabetic patients

Mammary duct ectasia:
- This is a chronic inflammatory condition that cause sub-areolar periductal inflammation
- The ducts become dilated and begin to produce a protein-rich secretion
    - This usually causes a nipple discharge
- If untreated the ducts become obliterated due to chronic inflammatory processes
- Histologically these lesions will show chronic inflammatory cells surrounding ducts, with evidence of protein secretions in the form of foamy macrophages, calcified material or cholesterol crystals

Fat necrosis:
- This is a standard necrotic process that occurs within the fat tissue of the breast, usually secondary to trauma or other pathology
- Patients will present with a firm and palpable lump in the breast

- Histologically there will be evidence of necrotic tissue along with foamy macrophages
    - Foam originates in the digested fat
- Can clinically and mammographically mimic breast malignancies

NIPPLE DISORDERS

Inverted nipple:

- This is usually a condition present since birth, but can also be induced by fat necrosis, trauma or cancers
    - Any new onset inversion should be subject to further investigation
- No direct pathological link but can make breastfeeding difficult

Paget's disease:

- Breast cancer that affects the skin of the nipple causing a scaly or crusty appearance
    - Often looks like eczema
- Caused by malignant cells moving upwards and outwards from the underlying dermis
- Histologically malignant cells known as 'Paget cells' can be seen throughout the epidermis
    - These are large pale cells that are obvious
- The surface of the epithelium on histology will also appear thickened
- Important to differentiate from breast eczema

PROLIFERATIVE BREAST DISORDERS

Fibrocystic change:

- This is a condition wherein the lobules of the breast become dilated and cystic
- The stroma surrounding the lobules becomes dense and collagenous
- This condition is associated with prolonged oestrogen exposure
- Epithelial hyperplasia and metaplasia can often be seen histologically

Radial scar/complex sclerosing lesion:

- This is a benign proliferative condition wherein the ducts undergo a cystic change or epithelial proliferation that causes an outward stellate-patterned growth
    - This can often result in tissue distortion
- Can clinically and mammographically mimic some forms of malignancy
    - It is usually differentiated from a malignancy by the presence of retained myoepithelial cells

Gynecomastia:

- This is the abnormal growth of the male breast tissue, forming either a diffuse enlargement or a firm, rubbery subareolar mass that is either bilateral or unilateral
    - Commonly the tissue is very tender
- It is most commonly seen in pubertal boys and older men >55
    - Generally, the condition will spontaneously resolve for younger boys and infants
    - Older men should be investigated further to rule out malignancy
- This can be caused by endogenous hormonal imbalance, systemic disorders or exogenous hormone use
- Histological appearance will show an increased number of ducts but no lobules as well as hyperplasia

Ductal hyperplasia:

- This a proliferative condition in which the epithelial cell lining of the breast proliferates, filling the ducts
    - This condition can occur by itself or in combination with other pathologies and may be found incidentally
- Atypical duct hyperplasia is an extension of this condition wherein the ducts are filled with cells that appear atypical
    - This increases the chance of carcinoma development greatly

BREAST CANCER

Breast cancer is a leading cause of cancer and a leading cause of death for women and can occur (less rarely) in men. Glandular tissue of the beast is often responsive to hormones such as oestrogen and progesterone. This is important for cause and treatment of some breast cancers.

Risk factors include:

- Increased menstrual cycles
- Oestrogen medications
- Radiation exposures
- BRCA1 and BRCA2 mutations
- ERBB2 gene mutation
    - Familial breast cancers account for around 5% of total breast cancers

Protective factors include:

- Early pregnancy
- Longer time spent breastfeeding

Ductal carcinoma in-situ/invasive ductal carcinoma

- Ductal cells grow unchecked into the lumen of the duct (in situ)
- Ductal cells eventually invade past the basement membrane (invasive)
    - If cells migrate through the ducts to the skin of the breast or nipple, they can cause Paget's disease
    - The cells will usually invade in nests or clusters
- This is the most common form of breast cancer

Lobular carcinoma in-situ

- Lobular cells grow within the lobules of the breast without invading the ducts
    - LCIS is not considered malignant but a risk factor for further cancer development
- Can invade the surrounding tissue and form invasive lobular carcinoma
    - The cells will invade as single cells rather than clusters

Breast cancer is staged using the TNM tumour staging method and graded based on histological differentiation.

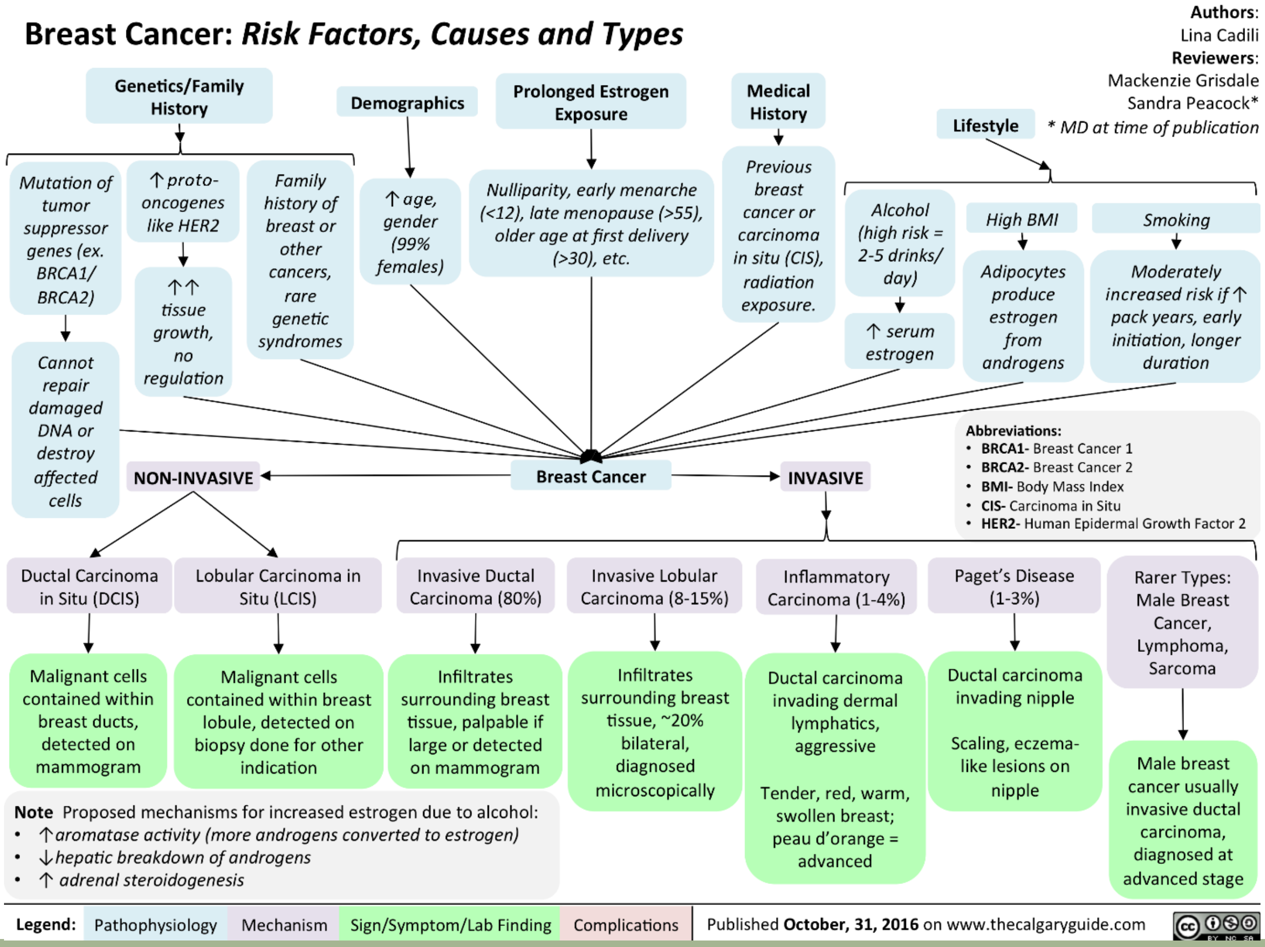
Breast cancer cells can be divided into:

- ER positive or negative
- PR positive or negative
- HER2 positive or negative

The prognosis of a breast cancer is dependent on:

- Stage – higher stage = worse prognosis
- Grade – higher stage = worse prognosis
- Status – more receptor positive = more targets for drugs = better prognosis
- Age of patient – older = worse prognosis

Treatment will usually involve a hormonal or chemotherapy regime to begin with but can also be treated with radiation as well as surgery.



Breast Cancer: ***Risk Factors, Causes and Types***

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Genetics/Family History
- *Mutation of tumor suppressor genes (ex. BRCA1/ BRCA2)* → *Cannot repair damaged DNA or destroy affected cells*
- *↑ proto-oncogenes like HER2* → *↑↑ tissue growth, no regulation*
- *Family history of breast or other cancers, rare genetic syndromes*

Demographics → *↑ age, gender (99% females)*

Prolonged Estrogen Exposure → *Nulliparity, early menarche (<12), late menopause (>55), older age at first delivery (>30), etc.*

Medical History → *Previous breast cancer or carcinoma in situ (CIS), radiation exposure.*

Lifestyle
- *Alcohol (high risk = 2-5 drinks/ day)* → *↑ serum estrogen*
- *High BMI* → *Adipocytes produce estrogen from androgens*
- *Smoking* → *Moderately increased risk if ↑ pack years, early initiation, longer duration*

Breast Cancer

NON-INVASIVE
- Ductal Carcinoma in Situ (DCIS) → Malignant cells contained within breast ducts, detected on mammogram
- Lobular Carcinoma in Situ (LCIS) → Malignant cells contained within breast lobule, detected on biopsy done for other indication

INVASIVE
- Invasive Ductal Carcinoma (80%) → Infiltrates surrounding breast tissue, palpable if large or detected on mammogram
- Invasive Lobular Carcinoma (8-15%) → Infiltrates surrounding breast tissue, ~20% bilateral, diagnosed microscopically
- Inflammatory Carcinoma (1-4%) → Ductal carcinoma invading dermal lymphatics, aggressive; Tender, red, warm, swollen breast; peau d'orange = advanced
- Paget's Disease (1-3%) → Ductal carcinoma invading nipple; Scaling, eczema-like lesions on nipple
- Rarer Types: Male Breast Cancer, Lymphoma, Sarcoma → Male breast cancer usually invasive ductal carcinoma, diagnosed at advanced stage

Abbreviations:
- **BRCA1-** Breast Cancer 1
- **BRCA2-** Breast Cancer 2
- **BMI-** Body Mass Index
- **CIS-** Carcinoma in Situ
- **HER2-** Human Epidermal Growth Factor 2

Note Proposed mechanisms for increased estrogen due to alcohol:
- *↑aromatase activity (more androgens converted to estrogen)*
- *↓hepatic breakdown of androgens*
- *↑ adrenal steroidogenesis*

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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MALE REPRODUCTIVE PATHOLOGY

MALE INFERTILITY

Male-cause infertility is involved in around 50% of cases presenting for ART. They are the sole issue in around 30% of cases.

Infertility refers to the inability to conceive after 12 months of normal, regular, unprotected sexual activity.

- Primary infertility refers to infertility with no previous pregnancies
- Secondary infertility refers to infertility with the history of previous pregnancies

Male infertility can be broken down into:

- Pretesticular: congenital or acquired disorders that affect the hypothalamus/pituitary/gonadal axis of control
  - Pituitary adenoma or disease
  - Exogenous anabolic steroids
  - Obesity
  - Hypogonadotropic hypogonadism
- Testicular: anything that affects the testes directly
  - Cryptorchidism
  - Varicoceles and other masses
    - Varicocele: This can contribute to subfertility via increasing the temperature of the testes due to venous reflux
      - These are cystic, hollow and trans-illuminated masses
      - Can be acquired or congenital
        - Congenital: due to incomplete obliteration of the processus vaginalis
        - Acquired: scrotal fluid collection usually occurring secondary to infection or trauma
      - Haematocele is the name given to a varicocele that contains blood (usually caused by trauma)
    - Spermatocele/epididymal cyst:
      - Transilluminable masses that occurs in the epididymis
      - Will often have a Chinese-lantern illumination pattern

            - Testicular cancers:
                - Germ cell tumours (95%)
                    - Seminoma: a painless, homogenous and malignant enlargement of the testicular tissues that occurs commonly in young men. On histology the mass will show evident inflammation and the testicular tissue will have a 'fried egg' appearance. The cancerous tissue will be hyperchromatic and may be encapsulated by the lobules of the testes.
                    - Non-seminomatous germ cell tumours:
                        - Yolk sac tumour: yellow, mucinous tumour that has Schiller-Duval bodies (appear like glomeruli)
                        - Choriocarcinoma: patient will have elevated hCG and positive pregnancy test along with possible gynecomastia and hyperthyroidism
                        - Teratoma
                        - Embryonal carcinoma: malignant and haemorrhagic with a poor prognosis, has obvious necrosis will sheets of undifferentiated and primitive gland like structures.
        - Klinefelter's syndrome
            - This is a common cause of undiagnosed male fertility characterised by the presence of a 47XXY chromosome. Patients will have:
                - Small testes
                - Infertility or subfertility
                - Tall stature and long legs
                - Absent or delayed puberty
                - Low muscle bulk, low facial hair, gynecomastia
                - Small penis
            - On investigation the patients will show:
                - Testicular atrophy (characterised by germ cell absence, high levels of Sertoli cells, peritubular fibrosis and interstitial fibrosis)
                - Reduced testosterone levels
                - Reduced or absent sperm levels
            - Diagnosis is made based on:
                - Karyotyping
                - Testicular biopsy
            - Treatment involves:
                - Exogenous testosterone
        - Inflammation or trauma
        - Iatrogenic
- Post-testicular: anything affecting the correct and normal ejaculation of sperm
    - Retrograde ejaculation
    - Ejaculatory duct obstruction

ASSISTED REPRODUCTIVE TECHNOLOGY

ART is the process of any technique that involves handling of sperm or oocytes outside of the body. It is used to help any couples who cannot naturally conceive. Normal fertility requires:

- Ovulation on a regular and predictable basis
- Adequate sperm delivered at the appropriate site and the right time
- Cervix to capture, nurture and release sperm
- Patent and functional fallopian tubes to transport sperm, ova and embryo
- Uterus to receive and support a pregnancy

There are many causes of subfertility. They include:

- Male causes: congenital, chromosomal, iatrogenic, lifestyle, sexual dysfunction etc.
- Ovulatory disorders: hypothalamic, pituitary, ovarian etc.
- Tubal defects: infection, surgery, endometriosis, ectopic pregnancy, appendectomy complications, congenital etc.
- Unusual problems: uterine factors, weight, female partner age, psychotherapy, donor ovum etc,
- Unexplained (accounts for around 10%)

IVF stands for in-vitro fertilisation and involves the following processes:

- Couple undergoes referral, assessment and counselling
- The ovarian reserve and semen quality of the partners are checked, the uterine cavity is imaged and both partners are checked for infectious diseases
- Ovarian hyperstimulation is induced with exogenous FSH
    - This causes the female to produce many eggs per cycle
        - An average IVF cycle will recover around 9 eggs, 7 of which are mature
    - This is monitored using blood tests and ultrasounds
- Trans-cervical ultrasound guided oocyte collection occurs
- The semen sample is provided
- Fertilisation of the egg occurs in vitro
    - A total of 6 eggs for every 7 will fertilise, and 4 will becoming dividing embryos
- The fertilised egg is transferred transcervically
    - This can occur on day 2 or day 5 post-fertilisation
- The remaining embryos are frozen
    - Usually 1 or 2 are frozen, and 1 or 2 are transferred

- Luteal phase support is given to the female partner
- The partner undergoes a pregnancy test two weeks later
- The couple repeat the process if the initial cycle is not successful with other frozen embryos

The success of IVF is influenced by:

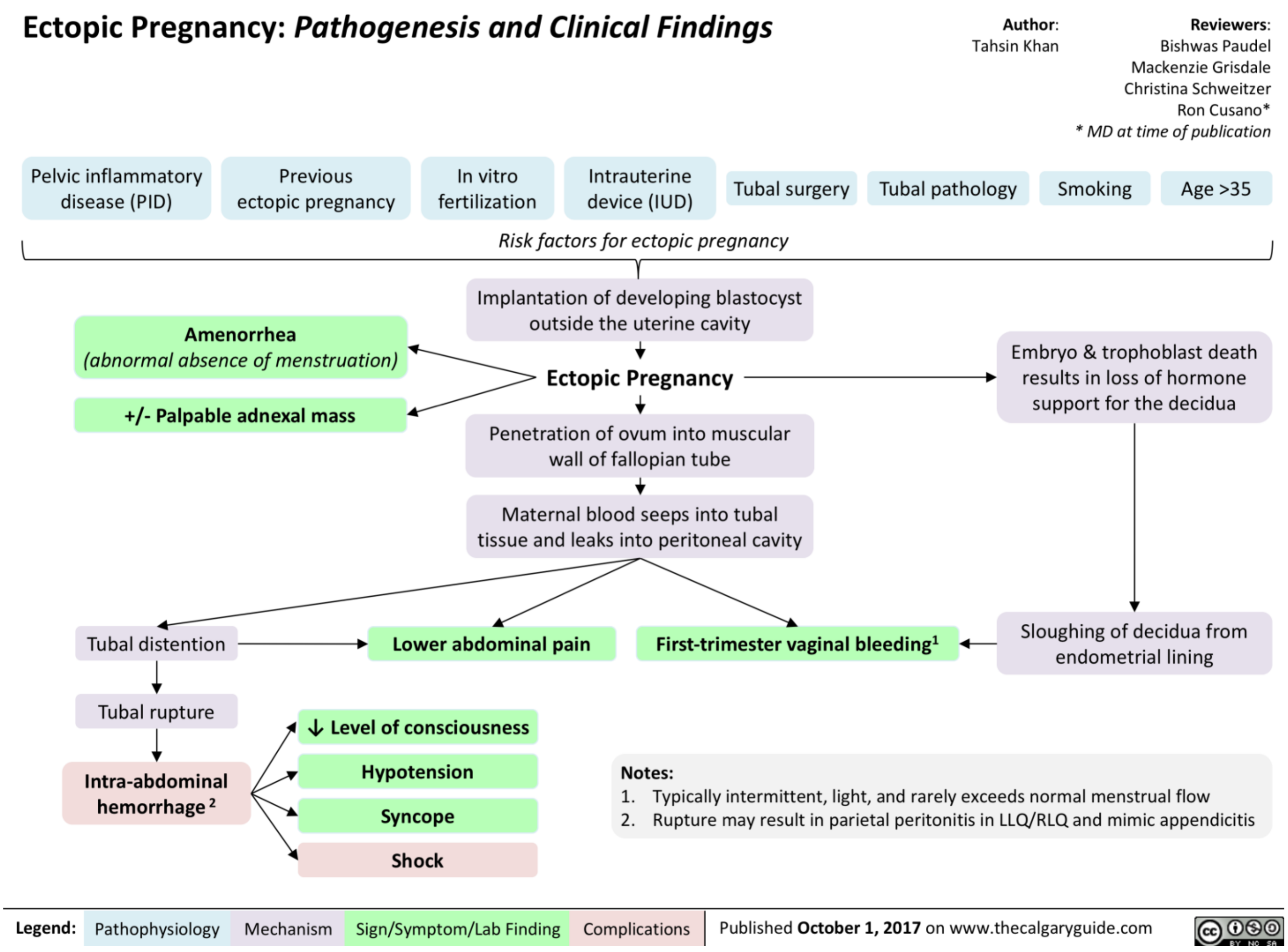
- The age of the female partner: success diminished with increased age
- Cause of infertility: higher success for male factor and tubal disease related infertility issues
- Genetic factors
- Lifestyle factors such as alcohol consumption and smoking
- Number of transferred embryos
  - The more embryos, the more likely the success of implantation
  - Increased embryo transfer also increases the likelihood of multiple babies
    - Twin pregnancies are undesirable because they have a higher complication rate and higher perinatal mortality rate
- Use of fresh vs frozen embryos: use of frozen embryos increases success of the treatment
  - This may be because it allows for genetic testing and single embryo transfer
- Day 2 vs day 5 transfer: Day 5 have higher success rates than day 2 transfers
  - Not all embryos can survive until day 5 in vitro

Complications of IVF include:

- Multiple pregnancy occurs frequently with multiple embryo transfer
- Ectopic pregnancies are more common (2x) in IVF
- Ovarian hyperstimulation syndrome
  - This is an excessive response to ovarian hyperstimulation that can cause thromboembolism, hypertension, nausea, vomiting etc.
- There is a marginally increased rate of miscarriage
  - This may be reflective of the population undergoing IVF rather than a result of IVF itself

PATHOLOGY OF PREGNANCY

ECTOPIC PREGNANCY



Ectopic Pregnancy: *Pathogenesis and Clinical Findings*

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Pelvic inflammatory disease (PID)
Previous ectopic pregnancy
In vitro fertilization
Intrauterine device (IUD)
Tubal surgery
Tubal pathology
Smoking
Age >35
Risk factors for ectopic pregnancy
Implantation of developing blastocyst outside the uterine cavity
Amenorrhea (abnormal absence of menstruation)
+/- Palpable adnexal mass
Ectopic Pregnancy
Embryo & trophoblast death results in loss of hormone support for the decidua
Penetration of ovum into muscular wall of fallopian tube
Maternal blood seeps into tubal tissue and leaks into peritoneal cavity
Tubal distention
Lower abdominal pain
First-trimester vaginal bleeding¹
Sloughing of decidua from endometrial lining
Tubal rupture
Intra-abdominal hemorrhage ²
↓ Level of consciousness
Hypotension
Syncope
Shock
Legend: Pathophysiology Mechanism Sign/Symptom/Lab Finding Complications

Notes:
1. Typically intermittent, light, and rarely exceeds normal menstrual flow
2. Rupture may result in parietal peritonitis in LLQ/RLQ and mimic appendicitis

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An ectopic pregnancy is any pregnancy in which implantation does not occur in the uterus. These are almost always medical emergencys and require surgical removal of the embryo to preserve the mother's life. Ectopic pregnancy and associated complications are still one of the leading causes of death of mother and foetus during pregnancy. This can include:

- Uterine tubes
  - This is the most common site
- Mesentery
- Ampulla

- Ovary
- Intestines
- Internal os

The symptoms of an ectopic pregnancy will vary depending on the site of implantation. Generally the symptoms include:

- Normal symptoms of early pregnancy
  - Nausea, vomiting, missed menstrual period
- Abnormal vaginal bleeding
- Lower abdominal pain
  - This is often severe and acute
- Lower hCG levels than a standard pregnancy
  - These are still elevated compared to non-pregnant women

Risk factors for ectopic pregnancy include:

- Ovarian tube damage
  - Pelvic inflammatory disease
  - Salpingitis
  - Abdominal surgery resulting in peritubal adhesions
  - Tubal ligation
  - Smoking
    - This is thought to contribute by causing damage to the cilia of the ovarian tubal cells
  - Altered tubal motility due to hormonal contraception
    - Progesterone only and IUD contraceptive devices are considered to be the major contributors to this
  - Infertility history
  - Assisted reproductive technology use
  - Maternal age

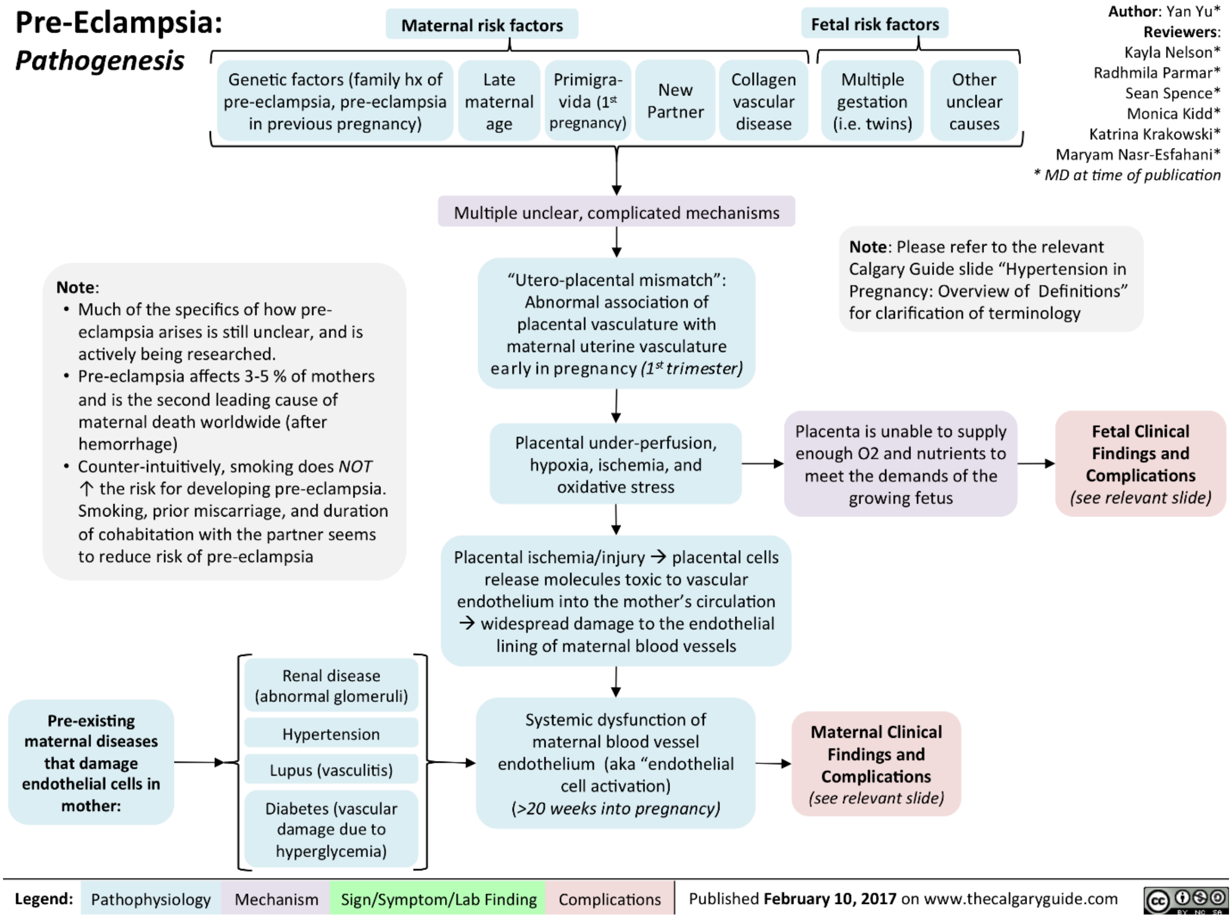
Complications of an ectopic pregnancy can be severe and life-threatening. However, if diagnosed and treated early they can be avoided. These include:

- Tubal or uterine rupture
  - Massive haemorrhage resulting in shock
  - DIC
  - Death

Treatments of ectopic pregnancy include:

- Surgical removal
- Methotrexate
  - This can cause regression of the placenta
  - This has a higher risk associated with it than surgical removal but is less invasive. For this reason it is only recommended for women with good health, no contraindications, an evidently non-viable pregnancy and the ability to return to emergency medical care if warning signs are suspected or recognised

PRE-ECLAMPSIA



Pre-Eclampsia:
Pathogenesis

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Maternal risk factors

- Genetic factors (family hx of pre-eclampsia, pre-eclampsia in previous pregnancy)
- Late maternal age
- Primigravida (1st pregnancy)
- New Partner
- Collagen vascular disease

Fetal risk factors

- Multiple gestation (i.e. twins)
- Other unclear causes

Multiple unclear, complicated mechanisms

"Utero-placental mismatch": Abnormal association of placental vasculature with maternal uterine vasculature early in pregnancy *(1st trimester)*

Placental under-perfusion, hypoxia, ischemia, and oxidative stress

Placenta is unable to supply enough O2 and nutrients to meet the demands of the growing fetus

Fetal Clinical Findings and Complications *(see relevant slide)*

Placental ischemia/injury → placental cells release molecules toxic to vascular endothelium into the mother's circulation → widespread damage to the endothelial lining of maternal blood vessels

Pre-existing maternal diseases that damage endothelial cells in mother:

- Renal disease (abnormal glomeruli)
- Hypertension
- Lupus (vasculitis)
- Diabetes (vascular damage due to hyperglycemia)

Systemic dysfunction of maternal blood vessel endothelium (aka "endothelial cell activation) *(>20 weeks into pregnancy)*

Maternal Clinical Findings and Complications *(see relevant slide)*

Note:

- Much of the specifics of how pre-eclampsia arises is still unclear, and is actively being researched.
- Pre-eclampsia affects 3-5 % of mothers and is the second leading cause of maternal death worldwide (after hemorrhage)
- Counter-intuitively, smoking does *NOT* ↑ the risk for developing pre-eclampsia. Smoking, prior miscarriage, and duration of cohabitation with the partner seems to reduce risk of pre-eclampsia

Note: Please refer to the relevant Calgary Guide slide "Hypertension in Pregnancy: Overview of Definitions" for clarification of terminology

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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The definition of pre-eclampsia is new onset hypertension during pregnancy accompanied by one or more of the following features: proteinuria, maternal organ dysfunction, haematological involvement or uteroplacental dysfunction. It is a common condition that afters women generally after 20 weeks gestation but has its pathophysiological origins in the first weeks of pregnancy. It most commonly presents in women after 34 weeks of gestation.

It is different from gestational hypertension, which does not have the associated features of pathology that pre-eclampsia does. Chronic hypertension is defined as hypertension diagnosed <20 weeks gestation or prior to pregnancy.

Pre-eclampsia can progress to eclampsia without treatment and can be life threatening for both the mother and the baby. Eclampsia is characterised by the onset of seizures and/or a coma.

Severe pre-eclampsia is considered a systolic > 160 and/or diastolic >110, while mild to moderate is considered systolic >140 and/or diastolic >90

Preeclampsia develops as a result of abnormal placentation.

- The spiral arteries of the decidua usually dilate and develop into uteroplacental arteries early in the pregnancy, but in pre-eclampsia the development of these arteries is abnormal.
    - The histological findings usually include narrowed and fibrous arteries, the cytotrophoblast invasion is less pronounced and maternal endothelial cells are still present
    - This is thought to occur due to poor immunoregulation on the maternal side
- Abnormal placental blood flow results in hypoxia for the foetus
    - This abnormal blood flow can also result from generalised hypoxia over a long-term period: it is thought that this can also result in pre-eclampsia
- The hypoperfusion of the placenta causes the release of pro-inflammatory mediators due to oxidative stress
- These inflammatory mediators can travel through the maternal circulation and cause endothelial dysfunction
    - Key features of maternal endothelial dysfunction include vasoconstriction and salt retention in the kidneys
        - These two features result in hypertension
    - Endothelial dysfunction can also cause vasospasm
        - Vasospasm in the kidneys can result in oliguria and proteinuria
        - Vasospasm in the retina can cause blurred vision and scotoma
        - Vasospasm in the liver can cause swelling, injury and stretching the liver capsule
            - This results in RUQ or epigastric pain, elevated LFTs and hepatic tenderness
    - Endothelial dysfunction can cause intravascular haemolysis and increased platelet use
        - This can result in intravascular coagulation alongside haemolytic anaemia
    - There is increased vascular permeability
        - This results in generalised oedema in the face and periphery
        - In the brain this can result in headaches, confusion and seizures when severe
        - In the lungs this can result in pulmonary oedema causing dyspnoea and cough

Risk factors for pre-eclampsia include:

- Increased maternal age
- Pre-existing hypertension
- Nulliparity
- Autoimmune disorders
- Obesity
- Pre-existing diabetes
- Family history of hypertension
- Low sperm exposure to paternal sperm
- Twin gestation
- Previous pre-eclampsia
- Previous stillbirth

Diagnostic factors include abnormal findings on normal maternal check ups or screenings in findings such as maternal blood pressure, maternal urine status etc.

Treatment of pre-eclampsia will depend on gestation age and the severity of the disease. The only curative method of treatment is surgical delivery of the baby, but ideally the baby should be maintained in utero until at term. Often women with pre-eclampsia are closely monitored and only undergo premature delivery if necessary.

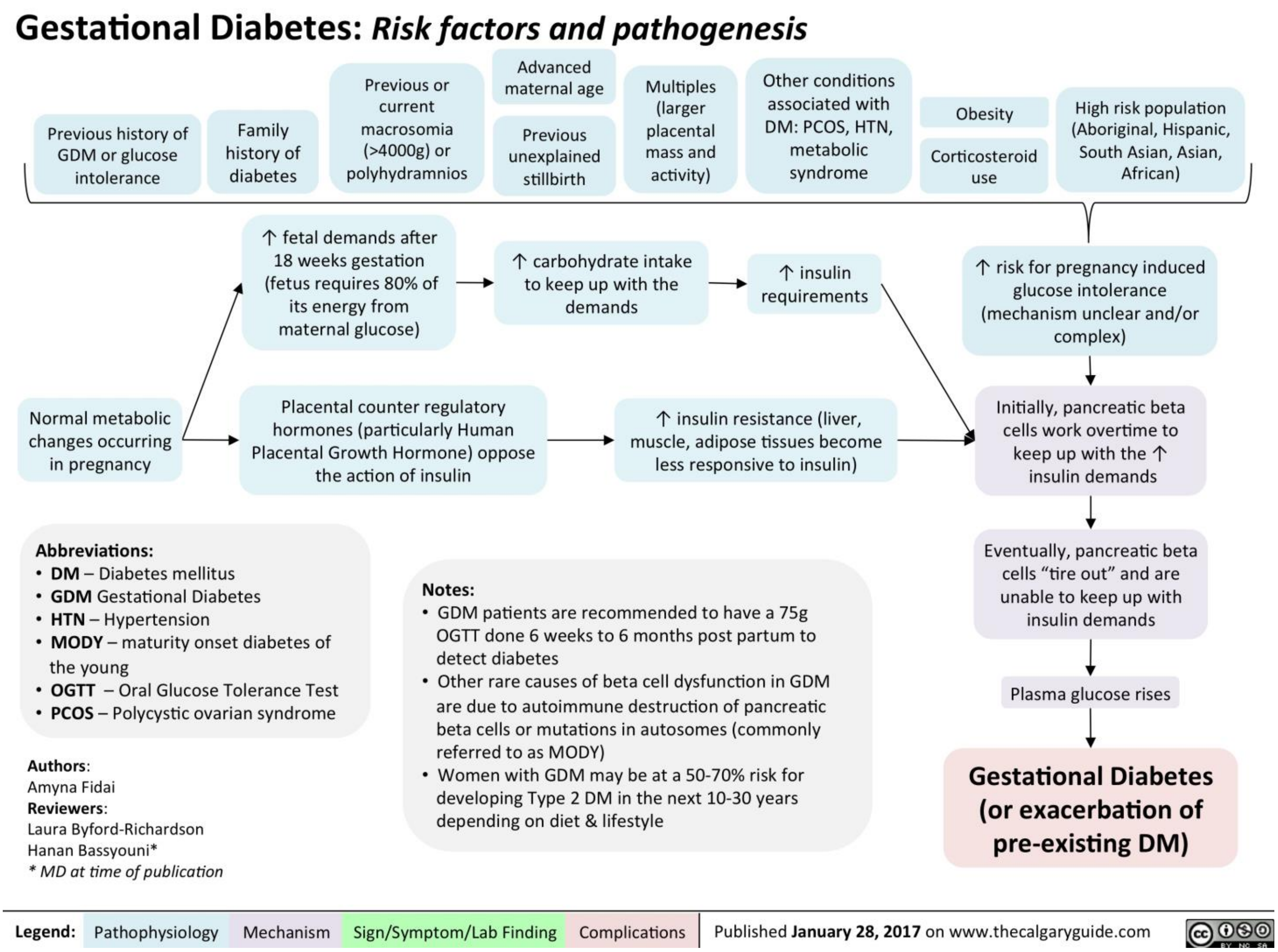
- Hospitalisation and delivery is usually indicated >37 weeks gestation
    - This is also indicated if the foetal weight is extremely low, if the maternal and/or foetal tests indicate severe disease or there is evidence of oligohydramnios
    - A vaginal delivery is preferred by c-sections are often required for cases of poor maternal/foetal condition or young gestational age
- Antihypertensive agents can be administered in severe hypertension cases
    - ACE inhibitors are ARBs are contraindicated in pregnancy
- Eclampsia is managed with standard emergency care as well as anticonvulsive therapy and the baby is delivered when mother is stable

Women who experience pre-eclampsia have an increased risk of developing hypertension and cardiovascular disease later in life, as well as generalised metabolic disease.

Complications of pre-eclampsia include:

- Placental abruption due to hypertension
- Strokes
- Renal failure
- DIC
- ARDS
- Foetal growth striction
- Seizure-induced foetal hypoxia
- Death of both mother and baby

GESTATIONAL DIABETES



Gestational Diabetes: *Risk factors and pathogenesis*

Previous history of GDM or glucose intolerance

Family history of diabetes

Previous or current macrosomia (>4000g) or polyhydramnios

Advanced maternal age

Previous unexplained stillbirth

Multiples (larger placental mass and activity)

Other conditions associated with DM: PCOS, HTN, metabolic syndrome

Obesity

Corticosteroid use

High risk population (Aboriginal, Hispanic, South Asian, Asian, African)

↑ risk for pregnancy induced glucose intolerance (mechanism unclear and/or complex)

Normal metabolic changes occurring in pregnancy

↑ fetal demands after 18 weeks gestation (fetus requires 80% of its energy from maternal glucose)

↑ carbohydrate intake to keep up with the demands

↑ insulin requirements

Placental counter regulatory hormones (particularly Human Placental Growth Hormone) oppose the action of insulin

↑ insulin resistance (liver, muscle, adipose tissues become less responsive to insulin)

Initially, pancreatic beta cells work overtime to keep up with the ↑ insulin demands

Eventually, pancreatic beta cells "tire out" and are unable to keep up with insulin demands

Plasma glucose rises

Gestational Diabetes (or exacerbation of pre-existing DM)

Abbreviations:
- **DM** – Diabetes mellitus
- **GDM** Gestational Diabetes
- **HTN** – Hypertension
- **MODY** – maturity onset diabetes of the young
- **OGTT** – Oral Glucose Tolerance Test
- **PCOS** – Polycystic ovarian syndrome

Notes:
- GDM patients are recommended to have a 75g OGTT done 6 weeks to 6 months post partum to detect diabetes
- Other rare causes of beta cell dysfunction in GDM are due to autoimmune destruction of pancreatic beta cells or mutations in autosomes (commonly referred to as MODY)
- Women with GDM may be at a 50-70% risk for developing Type 2 DM in the next 10-30 years depending on diet & lifestyle

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Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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Gestational diabetes is a condition similar to diabetes mellitus that occurs during pregnancy. Most mothers who develop GD are obese or overweight. There is a high risk of potential complications that can be adequately managed if diagnosed and detected early. It is a relatively common condition that occurs in up to 10% of all pregnancies

GD occurs due to diabetogenic hormonal changes that occur during pregnancy, increasing the mother's insulin resistance.

- The placental size increases and this causes increases in:
  - Oestrogen
  - Progesterone
  - Human placental lactogen
    - This hormone is responsible for decreasing maternal insulin tolerance and inducing lipolysis
  - Cortisol
- These hormones, the last two in particular, contribute to insulin resistance.
  - This is usually a physiological adaptation of pregnancy to ensure the baby has adequate glucose supply, while inducing increased free fatty acids for the mother to use instead.
- Maternal obesity or overweight can contribute because adipocytes release cytokines which can impair insulin signalling
- Maternal glycaemic control is thus impaired causing glucose to cross the placenta
  - Insulin from the mother does not cross the placenta
- The foetal pancreas develops and copes with high levels of glucose by producing large amounts of insulin
  - The foetus enters a state of hyperglycaemia and hyperinsulinemia
    - This results in increased fat and protein stores in the baby contributing to large gestational size or macrosomia
    - The fat and protein deposition usually occur in the shoulder and abdominal area
  - The foetus can also enter a state of hypoxia due to increased oxygen demands from increased glucose uptake and metabolism
- At delivery the baby is as risk of hypoglycaemia due to high levels of insulin and must be treated for this
- Macrosomia also often results in a complicated birth with increased risk of vaginal lacerations and necessity for c-section for the mother and, in vaginal birth, increased risk of shoulder dystocia, clavicle fractures and brachial plexus injury

Risk factors for GD include:

- Maternal obesity or overweight
- Previous gestational diabetes
- Previous macrosomia
- Family history
- Pre-existing type II diabetes or impaired insulin tolerance
- Recurrent pregnancy loss

Testing and screening for GD include:

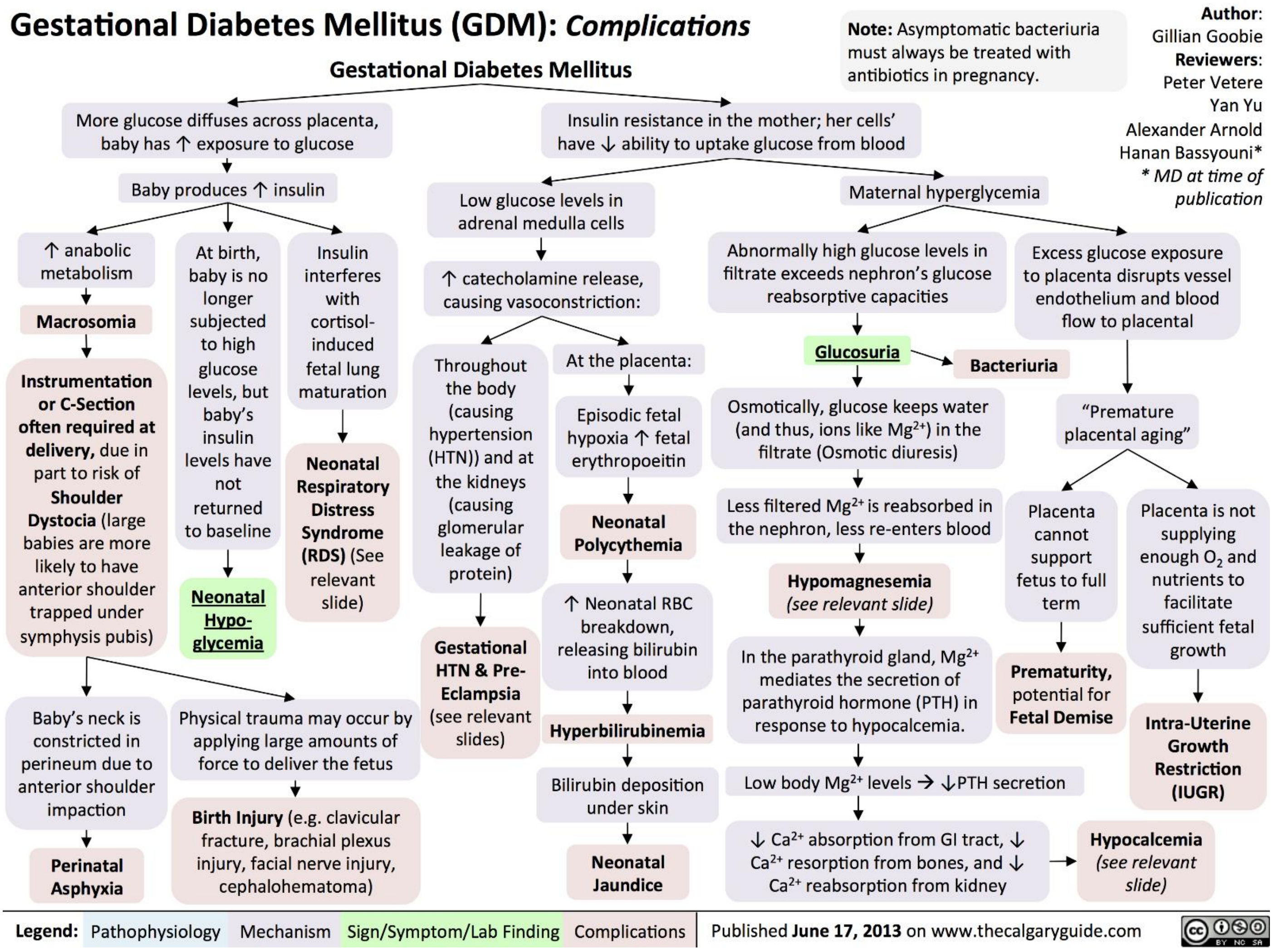
- Oral glucose tolerance test in the first and/or second trimester of pregnancy
    - This is usually only conducted in higher risk pregnancies
- OGTT is conducted for all pregnancies in the third trimester of pregnancy
    - An initial test involves a one-hour test
    - A confirmatory test conducted in abnormal findings includes a 3-hour OGTT
- Foetal macrosomia discovered on ultrasound or other test are indicative of further investigation

Treatment of GD involves:

- Lifestyle treatments to improve maternal glycaemic control
    - Dietary modification
    - Regular low-intensity exercise
    - Strict glucose monitoring
- Medications to improve glucose tolerance
    - Insulin is first-line therapy
    - Metformin is used if necessary
- Regular ultrasounds are conduced to monitor foetal growth and size

Complications of poorly managed or late detected GD include:

- Miscarriage
- Pre-eclampsia
- Birth difficulties resulting in both maternal and foetal injury due to macrosomia
    - The infant will have a normal head but increased shoulder circumference
        - This can progress to a difficult labour due to the head being delivered as normal but the shoulders being unable to progress
- Increased risk of congenital malformations



Gestational Diabetes Mellitus (GDM): *Complications*

Note: Asymptomatic bacteriuria must always be treated with antibiotics in pregnancy.

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Gestational Diabetes Mellitus

More glucose diffuses across placenta, baby has ↑ exposure to glucose

Baby produces ↑ insulin

↑ anabolic metabolism

Macrosomia

Instrumentation or C-Section often required at delivery, due in part to risk of **Shoulder Dystocia** (large babies are more likely to have anterior shoulder trapped under symphysis pubis)

Baby's neck is constricted in perineum due to anterior shoulder impaction

Perinatal Asphyxia

Physical trauma may occur by applying large amounts of force to deliver the fetus

Birth Injury (e.g. clavicular fracture, brachial plexus injury, facial nerve injury, cephalohematoma)

At birth, baby is no longer subjected to high glucose levels, but baby's insulin levels have not returned to baseline

Neonatal Hypo-glycemia

Insulin interferes with cortisol-induced fetal lung maturation

Neonatal Respiratory Distress Syndrome (RDS) (See relevant slide)

Insulin resistance in the mother; her cells' have ↓ ability to uptake glucose from blood

Low glucose levels in adrenal medulla cells

↑ catecholamine release, causing vasoconstriction:

Throughout the body (causing hypertension (HTN)) and at the kidneys (causing glomerular leakage of protein)

Gestational HTN & Pre-Eclampsia (see relevant slides)

At the placenta:

Episodic fetal hypoxia ↑ fetal erythropoeitin

Neonatal Polycythemia

↑ Neonatal RBC breakdown, releasing bilirubin into blood

Hyperbilirubinemia

Bilirubin deposition under skin

Neonatal Jaundice

Maternal hyperglycemia

Abnormally high glucose levels in filtrate exceeds nephron's glucose reabsorptive capacities

Glucosuria → **Bacteriuria**

Osmotically, glucose keeps water (and thus, ions like Mg^{2+}) in the filtrate (Osmotic diuresis)

Less filtered Mg^{2+} is reabsorbed in the nephron, less re-enters blood

Hypomagnesemia *(see relevant slide)*

In the parathyroid gland, Mg^{2+} mediates the secretion of parathyroid hormone (PTH) in response to hypocalcemia.

Low body Mg^{2+} levels → ↓PTH secretion

↓ Ca^{2+} absorption from GI tract, ↓ Ca^{2+} resorption from bones, and ↓ Ca^{2+} reabsorption from kidney → **Hypocalcemia** *(see relevant slide)*

Excess glucose exposure to placenta disrupts vessel endothelium and blood flow to placental

"Premature placental aging"

Placenta cannot support fetus to full term

Prematurity, potential for **Fetal Demise**

Placenta is not supplying enough O_2 and nutrients to facilitate sufficient fetal growth

Intra-Uterine Growth Restriction (IUGR)

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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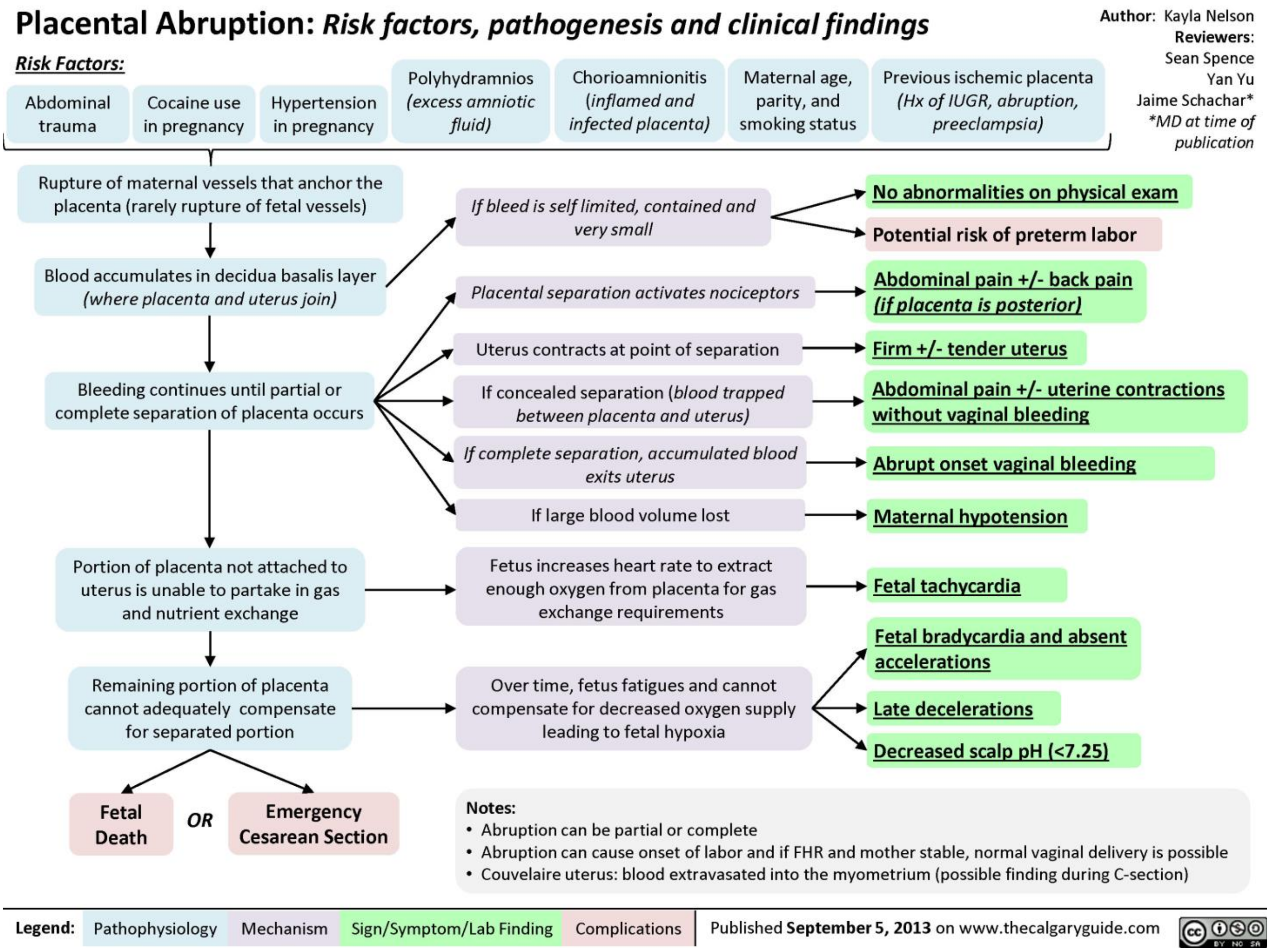
- This is more pertinent in the first trimester of pregnancy (more susceptible period) and therefore makes early detection of pre-existing impaired glucose handling or type-II diabetes important
- Polyhydramnios
- Vascular complications for the baby
- Increased risk of maternal type II diabetes, cardiovascular disease and metabolic syndrome later in life
- There is some evidence that macrosomia increased foetal risk of a number of conditions later in life

The diabetic state usually resolves are pregnancy, but women should be monitored in further pregnancies as well as having close attention paid to signs of type II diabetes due to increased risk.

PLACENTAL PATHOLOGIES

Placental pathologies usually arise during the third trimester of pregnancy.

Placental abruption



Placental Abruption: ***Risk factors, pathogenesis and clinical findings***

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Risk Factors:
- Abdominal trauma
- Cocaine use in pregnancy
- Hypertension in pregnancy
- Polyhydramnios *(excess amniotic fluid)*
- Chorioamnionitis *(inflamed and infected placenta)*
- Maternal age, parity, and smoking status
- Previous ischemic placenta *(Hx of IUGR, abruption, preeclampsia)*

Rupture of maternal vessels that anchor the placenta (rarely rupture of fetal vessels)

Blood accumulates in decidua basalis layer *(where placenta and uterus join)*

If bleed is self limited, contained and very small → **No abnormalities on physical exam**; **Potential risk of preterm labor**

Bleeding continues until partial or complete separation of placenta occurs

Placental separation activates nociceptors → **Abdominal pain +/- back pain *(if placenta is posterior)***

Uterus contracts at point of separation → **Firm +/- tender uterus**

If concealed separation (*blood trapped between placenta and uterus)* → **Abdominal pain +/- uterine contractions without vaginal bleeding**

If complete separation, accumulated blood exits uterus → **Abrupt onset vaginal bleeding**

If large blood volume lost → **Maternal hypotension**

Portion of placenta not attached to uterus is unable to partake in gas and nutrient exchange → Fetus increases heart rate to extract enough oxygen from placenta for gas exchange requirements → **Fetal tachycardia**

Remaining portion of placenta cannot adequately compensate for separated portion → Over time, fetus fatigues and cannot compensate for decreased oxygen supply leading to fetal hypoxia → **Fetal bradycardia and absent accelerations**; **Late decelerations**; **Decreased scalp pH (<7.25)**

Fetal Death ***OR*** **Emergency Cesarean Section**

Notes:
- Abruption can be partial or complete
- Abruption can cause onset of labor and if FHR and mother stable, normal vaginal delivery is possible
- Couvelaire uterus: blood extravasated into the myometrium (possible finding during C-section)

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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- This is a condition in which the placental detaches from uterus before delivery of the baby. It can occur in both a partial (minor separation) and complete (total separation) manner.
    - This causes haemorrhage from the uterus and the foetal vessels
        - This may be concealed in the mother if the placental abruption occurs in a position that prevents leaking of the blood through the vagina (concealed haemorrhage)
    - This results in foetal hypoxia and can result in intra-uterine growth restriction, premature birth or stillbirth
- Risk factors for placental abruption include:
    - Trauma
    - Smoking
    - Hypertension and preeclampsia
    - Cocaine use
- It is characterised by a dark vaginal bleeding (if apparent – bleeding can be hidden) as well as abdominal pain and uterine tenderness
- Foetal distress occurs in most cases
- Treatment involves monitoring the baby and child if stable
    - If unstable, emergency C-section can be conducted regardless of gestational age
- Complications include:
    - Intrauterine foetal death
    - Maternal haemorrhage and shock
    - Potential for uterine rupture if myometrial weakness and contractions are present

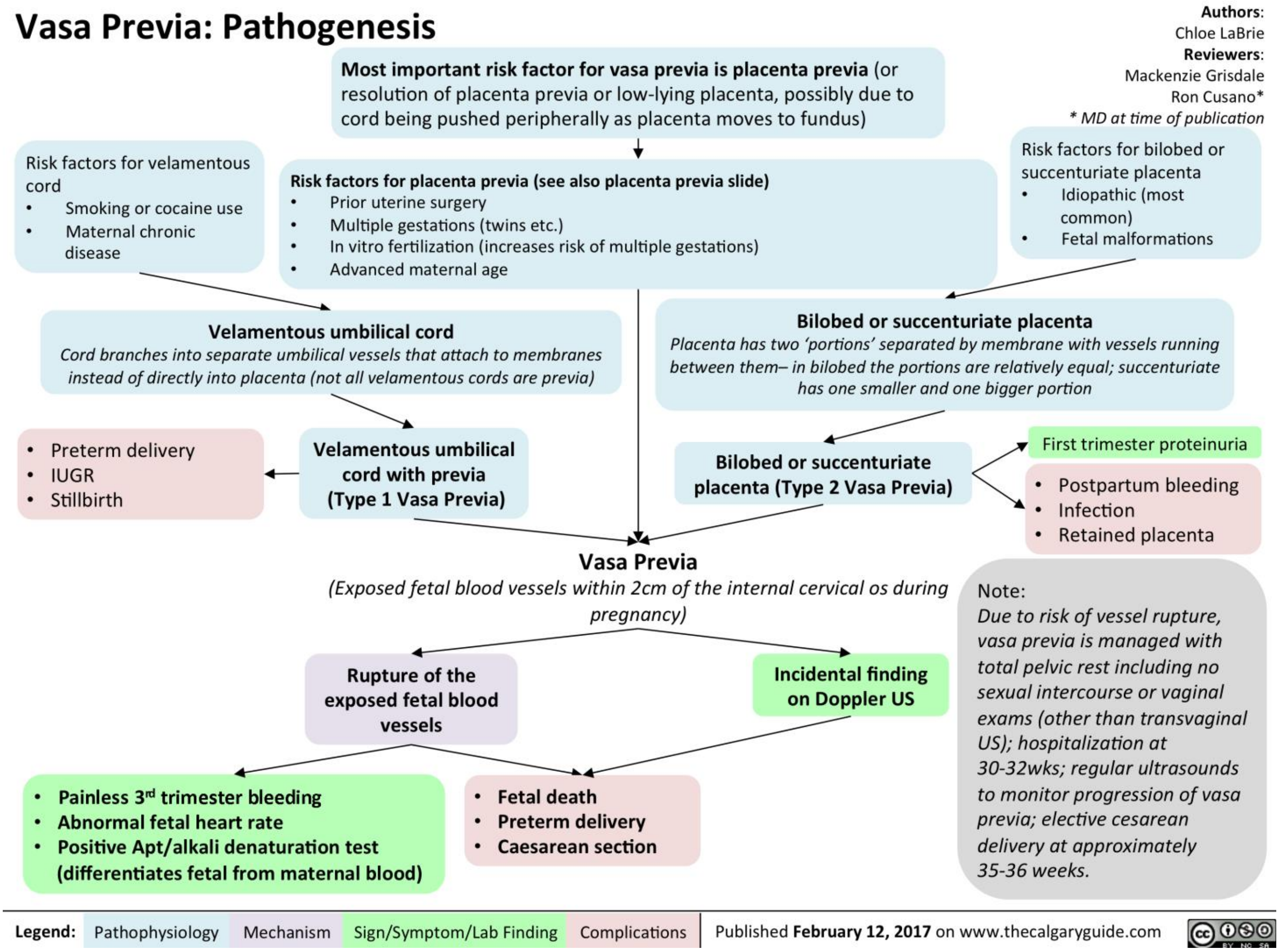
Placenta praevia

- This is a condition in which the placental either partially or completely blocks the uterine outlet (internal os) resulting in extreme haemorrhage during bleeding
    - Often this results in the need for c-section and can cause pre-mature delivery
- Its severity is often determined by how much of the os is covered by the placenta
- Risk factors include:
    - Multiparity
    - Increased maternal age
    - Prior c-section or curettage
- It is characterised by sudden, painless and bright red vaginal bleeding prior to the rupture of the membranes but usually does not cause foetal distress
- This is usually managed with monitoring the maternal and foetal health and C-section scheduled between 36-37 weeks of gestation

Placenta accrete/increta/percreta

- This condition occurs when the placenta grows too deeply into the uterine lining, making detachment of the placenta after delivery difficult or impossible. It can be categorised into:
    - Placenta accrete: the placenta encounters the myometrium
    - Placenta increta: the placenta grows into the myometrium
    - Placenta percreta: the placenta grows through the myometrium
- This can cause extreme haemorrhage during delivery and may result in premature birth
    - The retained placental tissue can sometimes result in the need for hysterectomy
    - Retained placental tissue can result in infection post-partum

Vasa praevia



Vasa Previa: Pathogenesis

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Most important risk factor for vasa previa is placenta previa (or resolution of placenta previa or low-lying placenta, possibly due to cord being pushed peripherally as placenta moves to fundus)

Risk factors for velamentous cord
- Smoking or cocaine use
- Maternal chronic disease

Risk factors for placenta previa (see also placenta previa slide)
- Prior uterine surgery
- Multiple gestations (twins etc.)
- In vitro fertilization (increases risk of multiple gestations)
- Advanced maternal age

Risk factors for bilobed or succenturiate placenta
- Idiopathic (most common)
- Fetal malformations

Velamentous umbilical cord
Cord branches into separate umbilical vessels that attach to membranes instead of directly into placenta (not all velamentous cords are previa)

Bilobed or succenturiate placenta
Placenta has two 'portions' separated by membrane with vessels running between them– in bilobed the portions are relatively equal; succenturiate has one smaller and one bigger portion

- Preterm delivery
- IUGR
- Stillbirth

Velamentous umbilical cord with previa (Type 1 Vasa Previa)

Bilobed or succenturiate placenta (Type 2 Vasa Previa)

First trimester proteinuria

- Postpartum bleeding
- Infection
- Retained placenta

Vasa Previa
(Exposed fetal blood vessels within 2cm of the internal cervical os during pregnancy)

Rupture of the exposed fetal blood vessels

Incidental finding on Doppler US

- **Painless 3rd trimester bleeding**
- **Abnormal fetal heart rate**
- **Positive Apt/alkali denaturation test (differentiates fetal from maternal blood)**

- **Fetal death**
- **Preterm delivery**
- **Caesarean section**

Note:
Due to risk of vessel rupture, vasa previa is managed with total pelvic rest including no sexual intercourse or vaginal exams (other than transvaginal US); hospitalization at 30-32wks; regular ultrasounds to monitor progression of vasa previa; elective cesarean delivery at approximately 35-36 weeks.

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications | Published **February 12, 2017** on www.thecalgaryguide.com

- This condition occurs when the umbilical cord lies over the internal os the uterus
    - This can cause injury of the vessels if the membranes rupture
- Risk factors include:
    - Bilobate or bisuccenturiate placenta
        - This occurs when the umbilical vessels with within the membranes relatively unprotected
        - Bilobed placenta occurs when there is two placentas present connected by vessels
    - Velamentous umbilical cord insertion
    - Placenta praevia
    - IVF
- It is characterised by painless vaginal bleeding occurring after rupture of the membranes
- It will commonly cause foetal distress
    - This condition can result in a tearing of the vessels and stillbirth in many cases
- Emergency C-section is indicated if foetal distress is evident

Placental infections
- The placenta, membranes and amniotic fluid are all susceptible to infection. Infection can be:
    - Ascending through the birth canal
        - This is more common
        - Usually bacterial
        - This can cause premature membrane rupture, pre-term delivery, pneumonia, meningitis and sepsis in the infant
            - This occurs because the prostaglandins can make the membranes weak
        - It is characterised by an acute inflammation of the placenta and membranes
    - Haematogenous transplacental spread of infection
        - Less common
        - Usually caused by:

            - Toxoplasmosis
            - Listeria
            - TB
            - Syphilis
            - Rubella
            - CMV
            - HSV
        - The organism causing the infection is the key determinant of complications, but they can include:
            - Foetal loss
            - Stillbirth
            - Congenital abnormalities
            - Haemolytic anaemia
        - It is characterised by chronic inflammation in the chorionic villi

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease includes both molar pregnancies (hydatidiform moles – complete and partial) as well as gestational choriocarcinoma and arise from the abnormal fertilisation of the ovum.

Molar pregnancy

- Complete mole:
    - Complete moles are diploid (usually XX, but some XY) with entirely paternal chromosomal content. They are the result of the fertilisation of an empty ovum with a sperm that undergoes spontaneous duplication of its chromosomes.
        - They can also be caused by dispermy of an empty ovum, but this is less common (10%)
    - Complete moles are more common than partial moles
    - They form a large, strangely shaped mass that fills and causes distention of the uterus
    - There is an absence of any embryonic tissue within the mole
    - It takes on the appearance of a bunch of grapes with hydropic villi that can be seen macroscopically
        - On ultrasound this is often referred to as a 'snowstorm' appearance
    - These are higher risk than partial moles
        - Complete moles have a 15% change of developing into choriocarcinoma
    - One complete molar pregnancy increases the risk of further molar pregnancies
    - Histologically the appearance is:
        - Hydropic (enlarged or distended) chorionic villi
        - Atypical trophoblastic proliferation characterised by nuclear atypia
- Partial mole
    - These arise from two sperm fertilising a single ovum and contain both maternal and paternal chromosomal content.
    - The anatomical changes that occur in a complete mole also occur in a partial mole but will not affect all of the tissue
        - There will be a dual population of normal villi along with hydropic villi, irregular scalloped contours and trophoblast inclusions and hyperplasia.
    - Foetal tissue is usually still present, but the foetus is not viable
    - Partial moles account for around 20-40% of total molar pregnancies
    - There is a lower chance of progression to choriocarcinoma
- Invasive mole:
    - This occurs when the trophoblasts invade the myometrium of the uterus causing in increased bleeding risk and increased changes of haematogenous spread.

Risk factors for molar pregnancy include:

- Miscarriage history
- Maternal age
- Prior molar pregnancy

Clinical features of molar pregnancy include:

- Complete mole:
    - Abnormal first trimester bleeding
    - Increased uterine size
    - Vesicle passage through the vagina
    - Greatly increased hCG level (compared to normal for gestational age)
- Partial mole:
    - Vaginal bleeding
    - Pelvic tenderness
    - Increased hCG level but lower compared to complete mole

Almost all hydatidiform moles are removed via curettage. It is important to follow patients up on a regular basis to monitor hCG levels due to the high risk of progression to invasive disease. This involves the monitoring of hCG levels to ensure lowering. The follow up regime is more stringent and occurs for longer following complete moles, due to the higher risk. Chemotherapy is indicted if hCG levels do not decrease or if metastases are evident

Choriocarcinoma refers to a highly aggressive and malignant tumour of trophoblastic tissue. This occurs very rarely after gestation, but 50% are preceded by a complete molar pregnancy. The other 50% are composed of post-mismarriage or ectopic pregnancy or from normal pregnancy.

On histology the tissue will appear:

- Widely invasive with no evident architecture
- Haemorrhagic
- Cytotrophoblast and syncitiotrophoblast tissue not arranged into villi

Patients will present with:

- Abnormal vaginal bleeding

- Lack of uterine regression post-delivery
- Symptoms related to metastasis (variable)

Diagnosis is usually based on hCG levels (which will be extremely high), pelvic ultrasound etc.

Treatment usually involves chemotherapy as the cancer is highly responsive to this. Hysterectomy or other surgery can be conducted if necessary.

The cancer has a very good prognosis rate, with between 95-100% of patients making a full recovery.

EARLY PREGNANCY LOSS

This refers to the loss of a foetus or a miscarriage within the first 20 weeks of pregnancy. They can be both sporadic or recurrent and the incidence is difficult to determine due to the occurrence of unknown miscarriage. The causes can be both embryonic or maternal.

Spontaneous abortion refers to loss of pregnancy before 20 weeks gestation.

Stillbirth refers to the loss of pregnancy after 20 weeks gestation.

Embryonic causes include:

- Chromosomal abnormalities
  - This accounts for 50% of miscarriages and 70% of them occurring <7 weeks gestation
- Congenital malformation
- Multiple gestation
- Infection
- Blighted ovum

Maternal factors can include:

- Mechanical factors
  - Congenital uterine abnormalities
    - Septate uterus
  - Fibroids
  - Uterine adhesions
  - Cervical incompetence
- Immunological
- Toxin exposure
- Endocrine disorders
- Trauma
- Iatrogenic
  - Amniocentesis
  - CVS

Clinical features of a threatened abortion include foetal activity and vaginal bleeding. Usually if the abortion is inevitable, the bleeding will be accompanied by visible/palpable products of conception.

- Incomplete abortion occurs when there is retained products of conception within the cervical canal or uterus
- Hidden or missed abortion occurs when there is no bleeding, no expulsion of contents and no foetal activity

Diagnosis of spontaneous abortion usually include doppler ultrasound detection of absent foetal cardiac activity, which is often followed by transvaginal ultrasound. This is associated with downwards trending hCG levels.

Complications of pregnancy loss include:

- Familial mental health issues
- Septic abortion
  - Occurs when there is an infection of retained products of conception
- DIC
  - Occurs when retained conception products release thromboplastin into the circulation
- Endometritis

CONGENITAL DEFECTS

Teratogens are chemicals or conditions to which a mother can be exposed that can cause or increase the likelihood of development abnormalities in a child. These include a range of dangerous and severe drugs (i.e. cocaine, heroin etc.) to over the counter medications and conditions such as extreme heat. The time of development at which the foetus is exposed to the teratogen will often determine its effect and severity; the most sensitive period for development is considered to be the first eight weeks during which organogenesis occurs. Some teratogens can cause spontaneous abortion throughout pregnancy, too. The key categories of teratogens include:

- Infections: key infections with implications for the foetus include
  - Toxoplasmosis
  - Rubella
  - CMV
  - HIV
  - HSV-2
  - Syphilis
- Medications or chemicals
  - Thalidomide
  - Retinoic acid
  - Lithium
  - SSRIs
  - Warfarin
  - Alcohol
  - Mercury
  - Lead
  - ACE inhibitors

- Physical
    - Heat
    - X-Rays
    - Extreme exercise
- Hormones
    - Synthetic oestrogen
    - Maternal or gestational diabetes
    - Obesity

ANTERIOR BODY WALL DEFECTS

Defects of the anterior body wall occur due to failure of ventral body wall folding or development. They include:

- Umbilical hernia
    - Small protrusion of the bowel through the umbilical ring that is covered by skin
- Omphalocele
    - Persistence of the herniation of the abdominal contents into the umbilical cord
        - Sealed by the peritoneal layer of the umbilical cord
        - Around the 6th week of development, the GI contents grow very quickly, faster than the abdominal cavity can accommodate for: this causes midgut herniation through umbilical ring
        - Normally around week 10 the midgut will retract
    - The gut contents are sealed by the peritoneum and amnion
    - This can cause abnormal growth of the abdominal cavity as well as hypoxia of the abdominal organs through compression
    - Linked to disorders or trisomy
    - Risk increased with alcohol and tobacco consumption, SSRI use and obesity
    - Treatment involves post-delivery surgery
- Gastroschisis
    - Extrusion of the abdominal contents through the abdominal folds
        - This occurs because of a failure of lateral body wall folding in development, resulting in an opening of the anterior abdominal wall which extends from the exterior surface to the gut cavity
    - Usually occurs to the right of the umbilicus (not clear why)
    - The contents are not covered by amnion or peritoneum
        - This can cause irritation and inflammation which can result in malabsorption
    - Treatment involves post-delivery surgery and repair of the body wall defect
        - IV nutrients may also be considered

CLEFT LIP AND PALATE

Cleft lip and palate is one of the most common congenital disorders.

The primary palate is triangular in shape and is formed by the intermaxillary segment

- This is formed by the fusion of the medial nasal processes

The secondary palate is behind the primary and formed by two self-like outgrowths from the maxillary processes and are known as the palatine shelves.

- The palatine shelf should fuse in the midline at it grows outwards
- The palatine shelf should also fuse with the primary palate

Pathology of cleft lip and palate is an abnormality of the fusion of these structures.

- Cleft lip occurs when the superior part of the lip/philtrum did not fuse correctly
    - Pathology of the medial nasal processes (this forms the top lip)
- Cleft palate can be an abnormal fusion of the primary or secondary palate
    - Maxillary shelf development midline fusion
    - Maxillary shelf and medial nasal segment fusion

Often occur together because of the fact that the growth and fusion of the maxillary processes together drives the inward movement and fusion/formation of the intermaxillary segment.

Both cleft lip and palate can be bilateral or unilateral.

HEART DEFECTS

Defects in the development of the heart can lead to abnormal connections between the left and right hearts. This causes a right to left shunt in cyanotic conditions, causing blood to enter the left heart from the right resulting in mixing of deoxygenated blood with oxygenated blood. This causes widespread hypoxia and cyanosis. In a acyanotic condition there is a left to right shunt and no cyanosis.

General features include:

- Blue babies (when cyanotic)
- Nail clubbing
- Exertional dyspnoea
- Failure to thrive

Tetralogy of Fallot: This is most common cyanotic heart defect

- Right ventricular outflow obstruction due to pulmonary valve stenosis
- Right ventricular hypertrophy
- Ventricular septal defect
- Overriding aorta

Tricuspid valve atresia:

- Absent or rudimentary tricuspid valve resulting in no blood flow between the right atrium and right ventricle
- Functional univentricular heart: right ventricle is usually hypoplastic causing left ventricular and atrial dilatation due to volume overload

Ventricular septal defect: Most common congenital heart defect
- Hole in the wall of the interventricular septum
    - Usually occurs in the membranous part
- Causes left to right shunting and RV volume overload
    - This results in RV hypertrophy and pulmonary hypertension

Atrial septal defect:
- Impaired growth of resorption of the atrial septa (can be ostium primum or ostium secondum)
- Low pressure, low volume, left to right shunt
    - Usually asymptomatic (depending on size of the defect)

Patent ductus arteriosus:
- Failure of the ductus arteriosus causing left to right shunt and volume overload of the pulmonary vessels

Coarctation of the aorta:
- Narrowing of the aorta at the aortic isthmus
- Can be caused by intrauterine ischemia resulting in medial thickening and intimal hyperplasia forming a ridge around the aorta lumen
- This causes increased proximal flow and decreased distal flow
- Results in myocardial hypertrophy as compensation

NEURAL TUBE DEFECTS

Neural tube defects occur in a range of severities and are a result of failure of the formation/closure etc of the neural tube. This causes a failure of mesodermal organisation over the surface of the spinal cord in the region.
- Spina bifida: this is a birth defect wherein the left and right tissue of the spinal segments that usually protect the spinal cord (vertebral arches) do not fuse correctly forming an opening in the middle back.
    - Occulta: the neural tube defect is asymptomatic and closed but some vertebrae are not entirely closed
        - Most common
        - Most mild
        - No protrusion of tissue or forcing of tissue into spaces where they shouldn't be
        - Often diagnosed incidentally
        - May have hair, dimples or a birth mark above the site of the lesion
    - Meningocele: the meninges (filled with CSF) protrude through a defect in the skull or spine but do not contain spinal cord contents
        - Sometimes called meningeal cyst
        - Least common form
        - No damage to the spinal cord: no severe symptoms
    - Myelomeningocele: the neural tube defect is severe enough to lead to the extrusion of the spinal cord through the skin with or without meninges covering it
        - This is most severe
        - Usually occurs with the meninges: it is rare to see 'open' spina bifida
            - Exposed nerves cause serious damage and risk of infection to the nerves
        - Associated with Arnold Chiari II malformation
        - Prenatal surgery can be done to correct this but is risky
        - Post-natal surgery is done within first few days of life
- Craniorachischisis: the brain and spinal cord are completely open
- Anencephaly: open brain and lack of skull vault
- Encephalocele: herniation of the meninges and the brain
- Iniencephaly: occipital skull and spine defects causing extreme retroflexion of the head

Risk factors for neural tube defects occurring include:
- Folate deficiency
    - Can be addressed with folic acid supplements
    - However, developmental abnormalities usually arise during 4th week of pregnancy and thus mothers may not be aware of their pregnant status (and be taking supplement) at this stage
- Obesity
- Poorly controlled diabetes
- Medications

LIMB ANOMALIES

Limb anomalies can occur in a range of variations and at different stages of development, resulting in a varied presentation. Key categories include:
- Meromelia: lacking a part but not all of a limb (or multiple limbs)
- Amelia: lacking entire limb (or multiple limbs)
- Polydactyly: excess multiple fingers and/or toes
- Triphalangeal thumb: the thumb has three joints (three phalanges) and looks like a lot like a normal finger
- Syndactyly: having two or more fingers and/or toes wholly or partly fused by thin skin webbing
- Amniotic-band associated limb defects: strands of the amniotic sac separate and entangle developing parts of the body, causing growth constriction
    - Can affect the body wall and the head as well as the limbs

DIFFERENCES IN SEX DEVELOPMENT

Differences in sex development are relatively common and account for up to 12% of total congenital abnormalities. They can develop idiopathically or as a result of chromosomal abnormalities, gonadal dysfunction. Some examples of chromosomal DSDs include:
- Turner syndrome: 45x
    - This is a monosomy that causes a failure of sexual maturity in women
        - This can be easily treated with hormonal supplements

    - Individuals will be of normal intelligence but have a short stature
    - Most Turner syndrome patients are infertile
- Klinefelter syndrome: 47xxy
    - This is a trisomy that causes infertility and androgen deficiency in males
    - Individuals are often tall and have small testes but have normal intelligence
- Mixed gonadal dysgenesis/ovotesticular DSD: 45x, 46xy
- Chimeric/ovotesticular DSD: 46xx, 46xy
    - Ovotesticular DSD occurs when there is development of both ovarian and testicular tissue in the development of the foetus. It can be caused by chromosomal abnormalities as well as mosaicism.
    - 46xx DSD usually occurs as a result of congenital adrenal hyperplasia
        - Virilisation of the patient occurs due to drugs or maternal endocrine issues
        - Can also occur due to the translocation of the SRY gene to the X chromosome during spermatogenesis '
    - 46xy DSD occurs because of a 5-alpha reductase deficiency, deficient testosterone synthesis or complete androgen insensitivity syndrome.
        - These patients will have female external genitalia but testes

DEVELOPMENTAL PATHOLOGY

DEVELOPMENTAL DISABILITY:

Warning signs of developmental disability include:

- Month 1:
    - Doesn't suck
    - Doesn't blink in response to direct light
    - Doesn't focus and follow objects
    - Rarely moves arms
    - Floppy
    - Lower jaw tremble
    - No startle response
- Month 7:
    - Stiff or floppy
    - One hand reach only
    - Does not roll or turn over
    - Does not turn head
    - Does not babble
    - Difficulty moving objects to face or mouth
    - No spontaneous smile
- 12 months:
    - Does not crawl or drags one side when crawling
    - Cannot stand supported
    - Says no simple words
    - Uses no gestures
- 2 years:
    - Cannot walk or walks improperly
    - Cannot speak basic words or sentences
    - Does not know the function of common objects
    - No engaging in gaze, play, pointing etc
    - Does not follow simple instructions
- 3 years:
    - Frequent falling
    - Inability to make a block tower, difficulty drawing
    - Inability or difficulty communicating
    - No interest in other children

DELAYED AND PRECOCIOUS PUBERTY:

Precocious puberty occurs when the secondary sexual characteristics of the individual appear before the ages of 8 in females and 9 in males. It can be classified as:

- Central (true) precocious puberty: Elevated GnRH levels cause the premature activation of the HPG axis and cause early initiation of pubertal changes. This is also known as gonadotropin-dependant puberty and development is always isosexual.
    - Idiopathic
    - CNS lesions
    - Pituitary tumours
    - Inflammation and trauma
- Central (idiopathic) precocious puberty. Also known as gonadotropin dependant puberty without evident CNS abnormality.
    - This is more common in females.
- Peripheral precocious (pseudo) puberty: Precocious puberty without elevated GnRH levels. This is also known as gonadotropin-dependant puberty. The development can be isosexual or contrasexual.
    - Isosexual:
        - Ovarian tumours
        - Exogenous oestrogens (females)

    - Leydig cell tumours
    - CAH (males)
  - Contrasexual
    - Congenital adrenal hyperplasia (females)
    - Exogenous androgens (females)
    - Feminising adrenal tumours (males)
    - Exogenous oestrogens (males)

The clinical manifestations include:

- Development of all or some of the secondary sex characteristics
  - Central precocious puberty usually causes normal pubertal pattern
  - Peripheral precocious puberty may not follow normal pubertal pattern
- Accelerated growth and early skeletal maturity

Testing for precocious puberty includes:

- LH and FSH levels
  - Will be increased in central precocious puberty
- GnRH stimulation test
- Sex hormone levels
- Imaging
- Bone age testing

Treatment includes:

- GnRH agonist for central precocious puberty
  - This works because of superstimulation of the hypothalamus causing down-regulation of the receptors in the pituitary gland and decreased LH and FSH receptors
- Surgical removal of the causative tumour if relevant
- Cortisol replacement when cause by congenital adrenal hyperplasia

Delayed puberty can be both constitutional or pathological.

- Constitutional puberty occurs when there is no real reason for the delay, it just occurs at a later stage. This almost always occurs by 18 years of age.
  - This is the most common cause and may be genetically linked
  - No treatment is required as the individual will undergo puberty eventually
- Malnutrition or other chronic diseases: this causes impaired GnRH secretion
  - IBD
  - Chron's
  - Hypothyroidism
  - Psychosocial deprivation
- Hypogonadism
  - Hypertrophic hypogonadism: insufficient GnRH release causes insufficient LH/FSH secretion either in frequency or amplitude and can be congenital or acquired

Diagnosis of delayed puberty involves:

- Bone age investigation
- Basal LH and FSH levels
  - TSH and prolactin levels should also be included in a primary amenorrhoea case

Treatment includes:

- Frequent monitoring
- Gonadal steroids if delay is severe

HORMONE SUMMARY

Hormone	Embryology	Anatomy	Function	Synthesis	Feedback
Thyroid	Follicular cells (endodermal origin) Parafollicular cells (neural crest) Develops from midline diverticulum between 1st & 2nd pharyngeal arch from thyroglossal duct Duct migrates downwards around 7 weeks	Two lobes connected via an isthmus on anterior surface larynx at C5-T1 Follicular cells arranged to form follicles filled with colloid Parafollicular cells (C-cells) in stroma Arteries: superior and inferior thyroid arteries Veins: superior, middle and inferior thyroid vein	Follicular cells produce T_4 and T_3 T_3 more active than T_4 because of receptor affinity Parafollicular cells product calcitonin Thyroid hormone increases in basal metabolic rate via increase glycogenolysis, gluconeogenesis, degradation of TAGs, increase HR etc. Important for foetal development Calcitonin decreases calcium levels in blood	Hypothalamic neurons ☐ TRH ☐ anterior pituitary via hypothalamic hypophyseal portal system ☐ GPCR on thyrotrophs ☐ TSH ☐ blood ☐ Follicular cells ☐ increased Na/I-transport, increased colloid synthesis, increased iodide oxidation etc ☐ thyroglobulin exported to colloid and combined with iodine ☐ MIT and DIT conjugated ☐ endocytosis ☐ proteolysis into T_3 and T_4 without thyroglobulin ☐	T_3 and T_4 negative feedback onto hypothalamic neurons and anterior pituitary thyrotrophs Dopamine decreases TSH secretion TBG increased by oestrogen and decreased by steroids – alters free vs bound ratio

				exocytosis ☐ transport to TBG	
Parathyroid	Derived from endoderm Upper – 4th pharyngeal pouch origin Lower – 3rd pharyngeal pouch origin Lower descend with thymus and more variable position because further to travel	Four small glands within pretracheal fascia on posterior surface thyroid gland Chief cells secrete PTH Oxyphil cells have no known function Arteries: inferior thyroid gland Vein: thyroid plexus	PTH increases osteoclast activity and decrease osteoblast activity, increases Vit D activation in kidney to increase calcium uptake in GIT, increases calcium reuptake and phosphate loss in kidney	Calcium-sensing receptor responds to calcium levels in blood by secreting PTH	Hypercalcemia inhibits PTH and increases calcitonin levels Hypocalcaemia increases PTH secretion and inhibits calcitonin levels
Adrenal Catecholamines	Medulla of adrenal gland derived from neuroectoderm Cortex of adrenal gland derived from intermediate mesoderm of the urogenital ridge Originally separate but the cortex envelops the medulla during development Foetal cortex develops during foetal life and regresses to form definitive cortex in adult	Located at T12 level Left crescent shaped and right pyramid shaped. Left behind pancreas and right close to IVC and bare area liver. Both attached to inferior diaphragm. Arteries: superior (branch inferior phrenic), middle (branch aorta) and inferior (branch renal) Veins: left suprarenal drains into renal, right into aorta	Neuroendocrine release of catecholamines (pre-synthesized for fast release) under pre-ganglionic autonomic control Increase adrenergic response – bronchial dilation, skeletal muscle activity, glycogenolysis		CNS regulation
Adrenal Cortex		Zona glomerulosa: most superior layer with cells arranged into glomeruli-like structures Zona fasciculata: middle layer with lipid-rich cells arranged into bundles Zona reticularis: inner layer with cells arranged into reticular network	Mineralocorticoids (aldosterone) cause increased Na+ reabsorption and increased K+ excretion to increase blood volume Glucocorticoids (cortisol) causes increased plasma glucose through proteolysis, lipolysis, increases BV sensitivity to catecholamines, increases BP Androgens important for sexual differentiation and development. <5% DHEA in males is from cortex, while oestrogen from ovary more important in females	Mineralocorticoids: glomerulosa cells contain aldosterone synthase and glomerulosa cells respond primarily to angiotensin II Glucocorticoids: CRH ☐ GPCR on corticotrophs ☐ ACTH ☐ cortisol Cortisol can also bind to MSH receptors on cells Synthesize and secrete DHEA and androstenedione Peripheral tissues can convert weak androgens into stronger ones	Mineralocorticoids (aldosterone) controlled by RAAS and increased when blood volume/BP/renal perfusion is low ACTH has small role in control of aldosterone release Cortisol feeds back onto hypothalamus and anterior pituitary to decrease levels 11b-hydroxysteroid dehydrogenase converts cortisol to cortisone to prevent cortisol affects on blood volume in kidney when high Androgen feedback mechanism not clear
Prolactin		Released from adenohypophysis of the pituitary gland. Connected to hypothalamus via hypophyseal portal system. Located in the pituitary fossa of the sphenoid bone, covered anteriorly and separated from optic chiasm by diaphragm sella. Arteries: superior and inferior pituitary hypophyseal arteries	Increases milk production from breast tissue	Diurnal secretion is normal, promoted post-birth and via sensory stimulation of breastfeeding	Increased by TRH, VIP, GnRH, serotonin etc Inhibited by dopamine
GH			Increases and promotes long bone growth and protein synthesis etc. Important for normal development	GnRH ☐ somatotrophs ☐ GH ☐ liver ☐ IGF1	IGF1 decreases somatotroph release of GH Somatostatin inhibits release
FSH			Sertoli cell spermatogenesis, follicle development in ovaries, increased oestrogen and progesterone production	GnRH pulsatile release from hypothalamus ☐ anterior pituitary ☐ FSH and LH release	Inhibin downregulates release at the anterior pituitary High levels decrease release via kisspeptin acting in the CNS to act on hypothalamus

		Veins: hypophyseal veins drain into cavernous sinus			(as no direct receptor in hypothalamus) Levels of oestrogen in the early follicular phase have downregulatory effect at the AP
LH			Leydig cell testosterone production, Theca cell oestrogen and progesterone production, control ovulation		Oestrogen levels downregulate GnRH release during early follicular phase Very high oestrogen levels upregulate LH release in the late follicular stage Testosterone levels downregulate directly on AP and via kisspeptin in hypothalamus Progesterone downregulates at AP directly and indirectly at hypothalamus
ADH	Neurohypophysis is of neuroectodermal origin	Connected to the hypothalamus via direct neuronal connections (neural bodies extend from hypothalamus to posterior pituitary)	Increased distal convoluted tubule water permeability, increased water reuptake and increased blood volume and pressure, decreased blood osmolarity	Produced by neurosecretory bodies in the supraoptic nucleus and the paraventricular nucleus and secreted by neuronal bodies extending through the infundibulum within the PA	Controlled largely by blood osmolarity
Oxytocin			Increased smooth muscle contraction of breast for milk let down Increased SM contraction of uterus in delivery		Sensory changes control release – suckling of breast or stretching of uterine wall